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THE MEDICAL CLINICS of NORTH AMERICA

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VITAMINS AND THE GENERAL PRACTITIONER*

R. A. GUY, M.D.†

AMONG the forty or more nutrients which are indispensable for the life of man, there are twelve or more known vitamins and undoubtedly others not yet isolated. These are ingested in the food. They cannot be manufactured by the cells from simpler substances. Although they act essentially as catalysts in the complex chemical processes of life, daily replenishment is needed not only during growth, but throughout life. The partial lack of any one of them interferes with growth and causes distorted metabolism. More severe or prolonged deficit causes anatomical changes. The total lack in time causes death. Both symptoms and signs vary with the speed and severity of depletion as well as with the outstanding deficit. When certain of these deficiencies or combinations of them have been frequent and severe in a community the resulting clinical syndromes have been called by special names and thought of as special "diseases," as pellagra, beriberi, scurvy and the like.

Recently the most striking symptoms and signs of some deficiency syndromes have been shown to be specifically related to a paucity of one or another vitamin, but it must be emphasized that, in man, *there is always more than one def-*

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TABLE 1
RECOMMENDED DAILY ALLOWANCES FOR SPECIFIC NUTRIENTS*
Committee on Food and Nutrition, National Research Council, May, 1941

	Calories	Protein, Gm	Calcium, Gm	Iron, Mg	Vitamin A, IU	Thiamine (B ₁), Mg, †	Ribo- flavin, Mg	Niacin	Ascorbic Acid, Mg †	Vitamin D IU.
Man (70 Kg) Moderately active Very active Sedentary	3000 4500 2500	70	0.8	12	5000	1.8 2.3 1.5	2.7 3.3 2.2	18 23 15	75	¶
Woman (56 Kg) Moderately active Very active Sedentary	2500 3000 2100	60	0.8	12	5000	1.5 1.8 1.2	2.2 2.7 1.8	15 18 12	70	¶
Pregnancy (latter half) Lactation	2500 3000	85 100	1.5 2.0	15 15	6000 8000	1.8 2.3	2.5 3.0	18 23	100 150	400-800 100-800
Children up to 12 years Under 1 year 1-3 years 4-6 years 7-9 years 10-12 years	100/Kg 1200 1600 1600 2000 2500	3-4/Kg 40 50 60 70	1.0 1.0 1.0 1.0	6 7 8 10 12	1500 2000 2500 3500 4500	0.4 0.6 0.8 1.0 1.2	0.6 0.9 1.2 1.5 1.8	4 6 8 10 12	30 35 50 60 75	400-800 ¶
Children over 12 years Girls, 13-15 years 16-20 years	2800 2100	80 75	1.3 1.0	15 15	5000 5000	1.1 1.2	2.0 1.8	14 12	80 80	¶
Boys, 13-15 years 16-20 years	1200 3800	85 100	1.1 1.1	15 15	5000 6000	1.6 2.0	2.1 3.0	16 20	90 100	¶

* Tentative goal toward which to aim in planning practical dietaries, can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins the requirements for which are less well known.

† One mg. of thiamine equals 333 IU. 1 mg. of ascorbic acid equals 20 IU.

‡ Requirements may be less if provided as vitamin A, greater if provided chiefly as the provitamin carotene.

§ Requirements given are for approximately 6 to 8 months. The amounts of protein and calcium needed are less if derived from breast milk.

¶ Needs of infants increase from month to month. The amounts given are for approximately 6 to 8 months. The amounts of protein and calcium needed are less if derived from breast milk.

|| Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.

¶ Vitamin D is undoubtedly necessary for older children and adults. When not available, from sunshine, it should be provided probably up to the minimum amounts recommended for infants.

icit, that foods are complex, and that total diets are even more complex. Furthermore, there are interrelationships between all nutrients, both during digestion and absorption and in their metabolism, so that a lack of one or more ingredients may interfere with the use of others which are present. The converse makes possible a great economy of use when the best possible "balance" of all nutrients is supplied. Note, for instance, the small amount of protein, 1.5 to 2 gm. per kilogram of body weight, which the infant needs during the first year of rapid growth, if it is the protein of human milk, compared to the much larger amount, 3 to 4 gm. per kilogram, needed if it is the protein of cow's milk presented to him in that food mixture. Moreover, with more protein to metabolize, he apparently needs more ascorbic acid (Dann, 1942). Compare the small amount of calcium, 0.34 gm. daily, needed if it is derived from human milk, with the large amount of 1.0 gm. daily if it is derived from cow's milk. Note the greater need for vitamin D in the latter case. The study of such synergisms and antagonisms is just beginning.

It is for the reasons given that insistence is made on the ingestion of the normal, general "well balanced" diet associated with vigorous health. This may consist of different foods in different parts of the world. It may be wholly vegetarian or wholly carnivorous, but when analyzed for fundamental nutrients will show their relative proportions to be much the same. Only the foods from which they are derived differ.

DAILY VITAMIN NEEDS

So-called daily needs are rough estimates of what a normal person in good health actually uses. Allowances recommended by the Committee on Food and Nutrition of the National Research Council in May, 1941, are shown in Table 1. The allowances for thiamine, riboflavin and niacin (nicotinic acid) are proportional to the caloric intake. This relationship has been established for thiamine and has been assumed for flavin and niacin because they, like thiamine, form part of the enzyme systems involved in the metabolism of carbohydrate. It is recommended that there be:

Thiamine	50 to 70	micrograms per 100 calories
Riboflavin	70 to 100	" " "
Niacin	500 to 800	" " "

In conformity with present American dietary habits a list of foods which will supply these essentials (Table 2) and an actual low cost menu for one day (Table 3) were published by the committee. Calories and vitamins are computed in Table 4.

TABLE 2

DIETARY "PATTERN" TO MEET THE RECOMMENDED ALLOWANCES

Milk, adults 1 pt., children 1½ pts. to 1 qt.
 Egg, 3 or 4 times per week.
 Meat, 1 serving (1 oz. at 1 year up to 3 oz. for adults).
 Vegetables, 2 servings. One green or yellow.
 Fruit, 2 servings. One citrus or tomato and one other, such as apple or prunes.
 Potato, one or more servings.
 Butter or oleomargarine fortified with vitamin A, 100 to 500 calories (½ to 2 oz.).
 Whole grain or "enriched" cereal and bread, at least half of the intake.
 Sugar, fat, etc., to complete calories.

Another menu using the same pattern but different foods is computed in Table 5, in which it is shown that the foods listed, if they provide 2000 calories, will provide 70 micrograms of thiamine per 100 calories, but if further energy to

TABLE 3

SAMPLE LOW-COST DIETARY

(As per Chicago Standard Budget, Costing 32 Cents per Day, Spring, 1941)

<i>Breakfast</i>	<i>Lunch</i>	<i>Dinner</i>
Tomato juice Oatmeal with top milk Toast with oleomargarine Coffee for adults Milk for children	Baked navy beans, baked without soda Cabbage salad, green, un- cut Bread with oleomargarine Prunes Milk	Pot roast and gravy Baked potatoes and oleo- margarine Gingerbread Tea or coffee for adults Milk for children

2500 calories is supplied by 4 ounces of sugar, the thiamine-calorie ratio will fall to 56 per 100 calories, and if the energy is increased to the 3000-calorie level by sugar and fats carrying no vitamins, there will be only 46 micrograms of thiamine per 100 calories, a thiamine level below that consid-

TABLE 4
CALORIE AND VITAMIN VALUES IN SAMPLE LOW-COST DIETARY FOR SPECIFIED INDIVIDUAL

Sex, male
Activity, moderate

Height, 180 cm. (6 ft.)
Weight, 70 Kg. (154 lb.)
Age, 30 years

Daily Needs		Food	3000	5000	75	1800	2700	50-70
1 dble Portion, Gm	As Purchased, Market Measure							
480	1 pint	Milk	310	500	0	210	1,000	Thiamine, Micrograms per 100 Cal.
100	1/2 lb	Meat, beef	150	50	0	120	225	Riboflavin, Micrograms
100	1/2 lb	Cabbage, raw, 1 c., bleached	10	0	0	80	10	
100	1/2 lb	Carrots, 3/4 c cubed	10	2,100	5	60	60	
200	7 oz	Tomato juice, canned	10	2,000	10	110	100	
200	7 oz	Prunes, dried (20)	600	5,000	1	100	100	
200	3/4 lb	Potatoes, 1 medium without skin	100	50	0	270	135	
100	3/4 lb	Beans, baked without soda	210	110	0	300	130	
60	8 T.	Onion, 1 1/2 c cooked	200	0	0	100	50	
50	6 slices	Bread, whole wheat or enriched.	520	0	0	10	30	
200	5 T.	Orange juice, large piece ...	500	2,600	0	0	0	
75		Oleomargarine (fortified)	250	0	0	0	0	
66		Sugar, jam, etc ...						
Total			3,380	12,180	79	2,020	1,970	60

T = tablespoonful; c = cupful.

TABLE 5
COMMON DAILY MENU SHOWING PROGRESSIVE THIAMINE DEFICIENCY AS ENERGY IS INCREASED BY FOODS CONTAINING NO THIAMINE

Height, ?
Weight, ?
Age, ?

Sex, ?
Activity, ?

Daily Needs		Food	Calories	Vitamin A, I.U.	Ascorbic Acid, Mg.	Thiamine, Micrograms	Riboflavin, Micrograms	Thiamine, Micrograms per 100 Cal.
Edible Portion, Gm.	As Purchased, Market Measure							
480	1 pint	Milk.....	310	480	0	240	960	
50	1 whole	Egg.....	80	500	0	75	160	
100	$\frac{1}{4}$ lb.	Meat, beef....	150	50	0	100	200	
100	$\frac{1}{4}$ lb.	Spinach.....	20	10,000	20	100	70	
100	1	Carrots.....	15	2,100	5	60	60	
100	$\frac{1}{4}$ lb.	Oranges, 1 medium	50	40	2	80	15	
100	$\frac{1}{4}$ lb.	Prunes, 10 medium	300	2,500	0	180	60	
100	$\frac{1}{4}$ lb.	Potato, 1 without skin...	100	30	0	90	45	
100	$\frac{1}{4}$ lb.	Butter, 4 T.....	410	1,200	0	0	30	
60	2 oz.	Oatmeal, $\frac{1}{4}$ c. cooked...	120	0	0	300	75	
30	1 oz.	Bread, $\frac{1}{2}$ whole wheat...	390					70
150	6 slices	Total	2,015	17,060	67	1,105	1,675	
		If calories are made up by sugar.	465	0	0	0	0	56
116	4 oz.	If calories are made up by sugar or fat ..	2,500					46
			500					
			3,000					

T. = table-spoonful; c. = cupful.

ered essential for vigorous health. In other words, a 3000-calorie diet will stand about 60 gm. (2 ounces) of fat and 60 gm. (2 ounces) of sugar, giving together 780 calories (approximately 26 per cent) which do not contain thiamine. Otherwise foods especially rich in thiamine, such as pork or dried legumes, must be included. Note that the diet in Table 4 contains more potato, beans and actually whole wheat bread, whereas one-half whole wheat, as usually sold in urban stores, is used in Table 5.

Table 6 shows a frequently used menu, which is inadequate not because of poverty. Note that meat is given at two meals, but that whole cereals, either as porridge or bread, are not included, and that the small amount of thiamine in white bread is further depleted by toasting. The thiamine-calorie relationship is far below the level for health; in fact it is that frequently associated with frank disease. Fortunately diets vary from day to day, but it is easily seen that anyone who selects this general pattern will rarely achieve an excellent diet. The use of "enriched" flour for the bread and pie would improve the thiamine intake slightly, providing 360 micrograms in the bread and 40 micrograms in the pie, totaling 400, or a thiamine-calorie ratio of approximately 33, still dangerously low. Aside from the paucity of B vitamins, both ascorbic acid and vitamin A are insufficient. Different vegetables and more fruit would rectify these.

Causes of Insufficient Supply of Vitamins in Diet

Insufficiency of any nutrient may be due to:

1. *Decreased intake* due to fashions, fads, special diets for allergy, diabetes, weight loss and so on, ignorance, poverty or famine.
2. *Decreased absorption, distribution, or use*, as in diseases of the gastro-intestinal tract, sprue, colitis, diarrhea, cardiovascular failure, liver disease.
3. *Increased loss* as in diarrhea, polyuria and sweating.
4. *Increased needs* as during growth, pregnancy and lactation, exercise, fever, hyperthyroidism.

TABLE 6

DAILY MENU FREQUENTLY CHOSEN BY WELL-TO-DO WOMEN, SHOWING DEFICITS OF ALL VITAMINS

Sex, female
Activity, housework

Height, 160 cm. (63 in.)
Weight, 56 Kg. (124 lb.)

Age, 25 years

Daily Needs	Food	2500		5000		70		1500		2200		50-70	
		Calories		Vitamin A, IU		Ascorbic Acid, Mg.		Thiamine, Micrograms		Riboflavin, Micrograms		Thiamine, Micrograms per 100 Cal.	
Paid Portion, Gm	As Purchased, Measure												
100	3 1/4 oz	50		200		10		80		15			
25	1 slice	65		0		0		9		0			
10	1/4 oz	73		200		0		0		0			
20	1/2 oz	80		0		0		0		0			
60	1 1/4	120		160		0		18		1			
	Orange juice												
	Brad, white, toasted												
	Butter, 1 pat												
	Sugar } In coffee, 2 c												
	(cream												
	Total	388		760		10		107		15 1/2		27	
	Brad, white, sandwich												
	Butter, 1 pat												
	Chicken, light, small slice												
	1 slice, blanched												
	Salad dressing, 1 T												
	Cheese, cream, 1 T												
	Crackers, small piece												
	Green, whipped												
	Sugar, 2 T												
	Cream, 2 T												
	Sugar, 4 T												
	Total	911		925		0		125		65		14	
	Meat, beef												
	Potato, 1 medium												
	Beets, 1/2 c diced												
	Butter, 3 pats												
	Pie, white												
	Roll, apple												
	Sugar, 2 T												
	In coffee, 1 c												
	(cream, 2 T)												
	Total	1181		860		2		270		265 1/2		42	
Daily total		2182		2615		42		502		115 1/2		20	
Percent		28		2155		28		998		185 1/2		40	

— = cal. insufficient, 1 = insufficient, 2 = rapid

Early Symptoms of Vitamin Deficiency

The first symptoms of any vitamin lack are the so-called *neurasthenic symptoms*—feelings of inadequacy, depression, irritability, apprehension (Jolliffe, 1938; McLester, 1939; Williams et al., 1940). The presenting or outstanding symptoms vary, not so much with the preponderating deficiency as with the individual's psychological make-up, what he expects of himself and how far he falls short of that expectation. He is trying to carry on as usual while lacking essential ingredients. The strain is felt. In many cases, these symptoms first appear when infection or other illness occurs, with pregnancy or lactation or with an extra load of work. The diet had been just sufficient for ordinary life, but not adequate to put by a store of nutrients for use in time of extra need. These symptoms are, of course, not specific or diagnostic and often have no relation to deficits of vitamins or other nutrients. However, they do demand investigation of the diet and rectification of any faults disclosed. The general practitioner has a particular opportunity to detect dietary faults before they have caused even these early symptoms and to prevent their appearance. In these early stages the only practicable diagnostic technic is *evaluation of the diet*.

EVALUATION OF THE DIET

In the case of infants and young children, an evaluation of the diet is usually made and specific directions are given. For older children and adults it is too often neglected, mainly because it is time-consuming. cursory questioning is rarely useful unless defects are gross. An ambulatory patient can bring a written record of everything consumed for at least a week, including, of course, alcohol and other drinks. On reviewing this record with the patient, the physician can check information concerning amounts and note whether he habitually eats with his family or in restaurants or institutions where foods are rarely freshly prepared and hence are impoverished as to vitamins. His likes and dislikes, fads and allergies can be noted, as well as whether the week recorded is typical of long-continued habits. Then a rough evaluation of his vitamin intake for the week can be made by reference to Table 7.

TABLE 7
VITAMIN CONTENT OF COMMON FOODS*

Food	As Purchased, Market Measure	Food	(chloride)	Vitamin A, I.U.	Ascorbic Acid, Mgr.	Thiamine, Micrograms	Riboflavin, Micrograms	Niacin, Micrograms
Apple (Wineapple)	1 small	Apple (Wineapple)	60	75	10	0	70	
Apple, sweet, sugar added	1/2 cup	Apple, sweet, sugar added	80	40	1	0	30	
Apple, fresh, 2 or 3	1 lb.	Apple, fresh, 2 or 3	56	4000	5	30	50	
" " " " "	1 lb.	" " " " "	200	4000	1	30	100	
" " " " "	1 lb.	" " " " "	90	4000	0	20	120	
Artichoke, globe, 1 large	1 lb.	Artichoke, globe, 1 large	60	100	14	180	1	
Asparagus, fresh, 1 lb.	1 lb.	Asparagus, fresh, 1 lb.	80		5	150		
" " " " "	1 lb.	" " " " "	26	700	35	200	160	
" " " " "	1 lb.	" " " " "	26	0	10	150		
Avocado, West Indian	1 lb.	Avocado, West Indian	20	0	10	70	60	
Bacon, medium fat	1 lb.	Bacon, medium fat	100	100	20	90	90	
Banana	1 small	Banana	100	300	0	100	100	
Barley, whole, 10 lb. raw	1 lb.	Barley, whole, 10 lb. raw	100	360	6	50	80	5700
" " " " "	1 lb.	" " " " "	160	0	0	160	10	
Beans, fresh, string or snap	1 lb.	Beans, fresh, string or snap	10	1000	0	100	0	
" " " " "	1 lb.	" " " " "	10	0	100	15	90	
" " " " "	1 lb.	" " " " "	100	500	10	15	100	
" " " " "	1 lb.	" " " " "	90	1000	25	200	160	
" " " " "	1 lb.	" " " " "	110	200	10	300	300	
" " " " "	1 lb.	" " " " "	150	100	0	150	900	
" " " " "	1 lb.	" " " " "	150	100	0	200	900	
" " " " "	1 lb.	" " " " "	150	100	0	300	900	
" " " " "	1 lb.	" " " " "	70	100	0	100	100	5000
" " " " "	1 lb.	" " " " "	10	700	1	30	1	
Beef, round, lean, chopped	1 lb.	Beef, round, lean, chopped	120	70	0	90		
" " " " "	1 lb.	" " " " "	100	70	0	90		
" " " " "	1 lb.	" " " " "	150	50	0	100		
" " " " "	1 lb.	" " " " "	200	90	0	100		
" " " " "	1 lb.	" " " " "	250	90	0	150		
" " " " "	1 lb.	" " " " "	10	1	0	0		
" " " " "	1 lb.	" " " " "	10	1	50	0		
" " " " "	1 lb.	" " " " "	100	50	2	50		
" " " " "	1 lb.	" " " " "	60	150	7	15		
Blackberry, 10 berries, 1/2 in. long	1 lb.	Blackberry, 10 berries, 1/2 in. long	60					

[illegible]

VITAMIN CONTENT OF COMMON FOODS—(Continued)

[illegible]

	lb	3 1/2 oz		lb	3 1/2 oz
Turnip, white, root, 1/2 c. cubed	30	0		30	0
" " yellow "	30	20		30	20
" " green "	30	10000		30	10000
Veal, calf, large serving	110	0		110	0
Walnut, English, kernels, 50	700	100		700	100
Watercress, 100 sprigs	20	4000		20	4000
Watermelon, 1/2 c. balls	50	0		50	0
Wheat, bran	200	120		200	120
" " cracked	350	15		350	15
" " cream of, 1/2 new	320	0		320	0
" " farina	350	0		350	0
" " farina	100	0		100	0
" " farina	170	0		170	0
" " puffed, 8 c.	360	0		360	0
" " Ralston's cereal	360	15		360	15
" " shredded, 3-lb. blacklts.	350	15		350	15
" " whole grain	350	0		350	0
" " flour, 60 per cent. extraction	250	0		250	0
Whiskey (brandy, 40, rum)	100	0		100	0

Vitamin values are expressed in round numbers for usual samples of food bought by urban stores. Most of the data have been taken from:

Blocher, L. B. and Hurley, B. R.: The Vitamin B₁₂ Content of Foods in Terms of Iron Intake. *J. Am. Diet. Ass.*, 49: 101, November, 1949.

U. S. Dept. Agric., Circ. 519, June, 1910.
Dried, J. P. and Muncie, H. E.: Vitamin Content of Foodstuffs. U. S. Dept. Agric., Misc. Pub. 275, June, 1937.
Muncie, H. E.: Vitamins and Their Occurrence in Foodstuffs. Milkmaid Memorial Fund Circulars, 28: 111, 1919.

Quarterly, 28, 331, 1916.
Report of Conell on Foinn and Nutrient of the American Medical Assn., J.A.M.A., 146: 2819 June 20 1911.
Washman, U. A. and Javeshjem, C. A.: The Vitamin Content of Meat, Burgess Pub. Co., Minneapolis, 1911.

In most cases $\frac{1}{2}$ pound of purchased yields, after waste has been discarded, 100 m. of collido material. When there is no waste a minus sign is placed after the

market measure, indicating that slightly less than 15 pound will give 100 gm. For a few foods the feedible waste is slightly more, in which case a plus sign is put after the market measure. If the waste is much more, as for corn on the cob, it is necessary to buy 35 pound to yield 100 gm. of edible food. In such cases the amount which must be purchased is indicated. Obviously the amount of waste varies greatly; it is sufficiently accurate for the present purposes to multiply each figure by 0.3. It is a great variation in all feeds, with, with variety, also, storage time and preparation methods, makes more precise calculations without significance. All measures are for uncooked food unless otherwise noted.

I.V. → International Units → U.S.P. units
 1 milligram → 1000 micrograms
 T. → teaspoonful → 15 cc.
 t. → teaspoonful → 5 cc.
 c. → cubic → 8 ounces by volume

In brackets are a few items in terms of usual acrylamide, as one egg.

VITAMIN CONTENT OF COMMON FOODS—(Continued)

Food Portion, Gm	As Purchased, Measure	Food	Calories	Vitamin A, I U.	Ascorbic Acid, Mg	Vitamin B, Micrograms	Riboflavin, Micrograms	Niacin, Micrograms
100	1 1/2 lb	Pumpkin, 1 medium	60	0	5	15	15	8000
100	1 1/2 lb	Pork, loin chop, broiled, 1 large	300	30	0	1100	210	
100	1 1/2 lb	Potatoes, new, skin eaten, 1	100	10	15	180	15	
100	1 1/2 lb	" " " " removed, 1	100	30	5	180	15	
100	1 1/2 lb	" " " " eaten, 1	100	30	5	90	15	
100	1 1/2 lb	" " " " removed, 1	100	30	0			
100	1 1/2 lb	" " " " cut and fried, 20 pieces, 2 3/4 lb by 2 3/4	100	30	0	180	60	
100	1 1/2 lb	Pumpkin, 10 medium	300	2500	2	50	50	
100	1 1/2 lb	Pumpkin, 1 1/2 c	10	2500	20	60	30	
100	1 1/2 lb	Raspberries, with seeds, 7 1/2	20	50	0	90		
100	1 1/2 lb	Raspberries, red, fresh, 3 1/2 c	70	0	0	0		
100	1 1/2 lb	Raspberries, fresh stems	20	0	5	0		
100	1 1/2 lb	Raspberries, stewed with sugar, 1 1/2 c	170	0	0	220	150	
100	1 1/2 lb	Rice, brown, whole grain	350	0	0	10	0	
100	1 1/2 lb	" " " " white, polished	360	0	0	200	10	
100	1 1/2 lb	Roe, fish, large serving	170	2000	5	100	100	
100	1 1/2 lb	Rutabaga, white, 3/4 c, cooked	110	0	10	75	100	12000
100	1 1/2 lb	" " " " yellow, 1/2 c, cooked	10	25	10	75	100	
100	1 1/2 lb	Rye, whole grain	350	0	0	160	10	
100	1 1/2 lb	Salmon, fresh, large serving	200	500	0	70	10	
100	1 1/2 lb	Salmon, canned, red	170	300	0	100	210	
100	1 1/2 lb	Sardines, canned in oil, 10 medium	200	0	0	30	10	
100	1 1/2 lb	Sauerkraut, 1 c	20	0	0	0	0	
100	1 1/2 lb	Sausages, pork	150	0	0	70	300	5000
100	1 1/2 lb	Soybean, green, dry	180	200	10	500	900	
100	1 1/2 lb	Squash, summer, 1 1/2 c, cooked	150	100	0	1200	100	
100	1 1/2 lb	" " " " winter	150	100	0	100	100	
100	1 1/2 lb	Squid, 1 lb	350	10000	20	100	10	
100	1 1/2 lb	Sweet potato, 1 small	20	1000	3	10	70	
100	1 1/2 lb	Tomatoes, 1 large	20	1000	10	0	0	0
100	1 1/2 lb	Tomatoes, red, fresh or canned	10	0	10	0	0	
100	1 1/2 lb	Turnips, 10 large	100	3500	20	100	30	
100	1 1/2 lb	Sugar, 7 1/2	120	150	10	100	30	
100	1 1/2 lb	Sweet potato, 1 small	50	1000	20	80	50	
100	1 1/2 lb	Turnips, 1 large	20	1000	20	70	50	
100	1 1/2 lb	Turnips, red, fresh or canned	20	1000	10	10	50	
100	1 1/2 lb	Turnips, red, fresh or canned	20	1000	10	10	50	

Because of the variability with season, variety, age, freshness and methods of cooking, precise measurements of food and drink and precise computations of ingredients are not possible. (When such is desired, aliquots of the diet must be analyzed.) Therefore, the values in Table 7 are expressed in round numbers and for the usual samples of food bought in urban stores.

The table is offered as a rough tool because a numerical expression, even with an error of plus or minus 10 per cent or more, is far more revealing than a qualitative one. For instance, eggs are listed as a "good source" of the B vitamins. However, one egg daily will supply only 75 micrograms of thiamine out of a needed 1500 to 2000. Butter is a "good source" of vitamin A, but if a thin film is spread on a piece of toast twice daily, using 10 gm. ($\frac{1}{2}$ oz.), only 200 of the needed 5000 units will have been eaten. One small orange, as the only source of ascorbic acid, will give only 40 mg. of the needed 70. In such ways are metabolic debts slowly piled up.

CORRECTION OF A VITAMIN DEFICIENT DIET

After an estimate of the patient's intake has been made, it can be compared with the allowances recommended in Table 1 for age and activity. If the patient is a sensible person and if the defects are slight or not of long standing, correction can be made by diet alone. With consideration for his likes and dislikes and economic resources, the physician can make out a fairly simple list of foods to be eaten daily. In order to repay metabolic debts as well as meet current expenditure, about *twice* the recommended allowances should be provided. Moreover, as the water-soluble vitamins are rapidly excreted, for economical use they should be taken with each feeding.

If any considerable fault in the diet has been present for some time, it is best to forbid all foods which do not contain vitamins, that is. all white flour and white cereals and foods made from them, such as macaroni, pie, cake, doughnuts; all sugar, jams, sweetened fruits and drinks. and alcohol. Care, of course, should be had that the other necessary nutrients not discussed here, such as protein, iron, calcium, as well as sufficient energy, are provided. The total energy of the diet can be decreased if loss of weight is desired or increased if

gain in weight seems best, by varying the amounts of whole cereals and potato, not by vitamin-free carbohydrates and fats.

If, however, the patient has any symptoms or signs referable to the deficiencies revealed by the diet record (Sebrell, 1940), if he is a food faddist with a capricious appetite, or if the major defects are those of the B vitamins, whose lack has a peculiarly devastating effect on normal appetite and gastro-intestinal functioning (Mackie et al., 1940; Mackie, 1941; Ruffin, 1941; Smith, 1940), it is probable that his bad feeding habits will be so firmly entrenched that persuasion as to proper diet will fail. In such a case, dietary improvements, always to be stressed, are best buttressed for a few weeks with more concentrated sources of the vitamins. During this time the desired foods should be gradually incorporated in the diet and the patient taught that when his deficiencies have been corrected, he will be able to "digest" many foods he thought he could not.

SPECIAL VITAMIN REQUIREMENTS IN CERTAIN DISORDERS

Not only because they are unable to eat all of the usual foods, but because their needs are increased, patients with the following disorders should have special attention to their vitamin intake, both in the diet and in extra form:

1. Febrile illnesses (Faulkner and Taylor, 1937).
2. Chronic illness, especially gastro-intestinal disorders, tuberculosis, cancer, cardiovascular disease (Weiss and Wilkins, 1937; Weiss, 1940).
3. Restricted diets, as for allergy and diabetes (Sydenstricker et al., 1939; Owens et al., 1940; Wilkinson et al., 1936).
4. Preoperative preparation (Bowman, 1937; Holman, 1940).
5. Water and dextrose therapy (Holman, 1940).
6. Convalescence (Bardett et al., 1942).
7. Alcoholic and drug addiction (Jolliffe, 1938).
8. Psychopathic disorders (Jolliffe, 1941).
9. All anemias.
10. Pregnancy and lactation (Ebbs and Moyle, 1942).

In all cases the diet itself should be planned to supply as much as possible. If a liquid diet is needed, milk, either whole, buttermilk, or skimmed milk, or "debuffered" milk (as lactic acid milk used in infant feeding) will probably form the basis

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1. *Wheat Germ*.—Wheat germ is the natural form, not further concentrated. It can be mixed with milk, soup or tomato juice or eaten as a cereal, or sprinkled on other cereal in place of sugar. It is not usually standardized and the freshness varies. Average commercial samples may be said to contain (some brands are richer):

Thiamine	25 micrograms per gm.
Riboflavin	8 " "

An ordinary portion would be:

Wheat germ, 14 gm. =	1 ounce by volume
	= ½ ounce by weight
	= 2 tablespoonfuls
	= thiamine, 350 micrograms
	= riboflavin, 110 micrograms

Various brands are available as: King Arthur, Battlecreek, Embo, Minneapolis Milling Company. Prices vary from 25 cents to \$1.00 a pound.

2. *Liver*.—Concentrates and extracts are usually made especially to supply the anti-pernicious anemia factor. The equivalence with fresh liver on the labels refers only to this activity. During extraction and concentration many substances are removed, notably thiamine. If liver concentrates are used in vitamin deficiencies, this must be provided for. For parenteral use such extracts are sometimes needed. The crudest, that is those with the fewest U.S.P. units of anti-pernicious anemia factor per cubic centimeter, are the richest in other vitamins; e.g.:

Liver Extract, crude (Lilly, old 343) for oral use.	
Anti P.A. factor	0.075 U.S.P. units per gm.
Thiamine	15.0 micrograms per gm.
Riboflavin	300.0 " "

This is a powder. About 70 gm. are needed to supply 1 mg. of thiamine, costing approximately \$3.50. For patients with severe pellagra, 70 to 100 gm. a day have been used.

Liver Extract, crude (Lilly, 352) for intramuscular injection.	
Anti P.A. factor	1.0 U.S.P. units per gm.
Thiamine	0
Other B vitamins	40 Sherman units

of the diet. It supplies the best of protein, as well as minerals and the B vitamins. Orange or tomato juices are palatable sources of vitamins C and A. Broths are liked and can be made so that they contain much ascorbic acid, if fresh green leaves are boiled in the bouillon for five to ten minutes only. One or another of these liquids can be given every two hours in amounts suitable to the patient's state and into them can be put the more concentrated sources of the water-soluble vitamins. As the patient can take more food, gruels and porridges made of the whole grain cereals (such bland combinations as "Pablum," "Cerevim," and "Gerber's Infant Cereal"—foods especially prepared for infant feeding and rich in B vitamins as well as protein and iron—are often useful), well cooked eggs, chowders of lean fish or meat and potato, well cooked stews, and liver. Mashed and chopped vegetables cannot be counted as potent sources of the water-soluble vitamins, which are largely destroyed by oxidation during such processes, but they have other nutrient values. Education of the patient to eat these needed foods is a major part of the treatment of vitamin deficiencies, whether slight or severe, and often calls for all the art and arts of medicine and nursing.

SOURCES OF VITAMINS MORE CONCENTRATED THAN ORDINARY FOODS

THE WATER-SOLUBLE VITAMINS

The B vitamins and ascorbic acid (vitamin C) will be considered first. They are particularly vulnerable to oxidative destruction during processing and cooking, and are also rapidly excreted in urine and sweat, even in the presence of tissue needs. Consequently, their inclusion with each meal is desirable. Especially in invalid diets attention must be given to the B vitamins, for aside from milk, most of the foods rich in these vitamins are considered rough and bulky, or hard to eat, such as whole grain cereals, legumes and meats.

B Vitamins

NATURAL SOURCES.—As the basis of all therapy with B vitamins, one of the natural sources known to contain all the members of this group should be chosen. There are three such sources.

In Table 8 are listed several of the well known brewer's yeast, with the amounts needed to supply thiamine. The green label Vegex powder is the most palatable has a strong hop flavor which has been eliminated in the label product. The Harris powder has more bulk than the others, and is almost tasteless. It contains more riboflavin and is marketed in unflavored mouthed 6-ounce bottles. Squibb's is the most granular. The Vegex paste tastes best because of its high flavor and salt content. It is measured (1 scant teaspoonful) and well mixed with water or tomato juice.

TABLE 8

BREWER'S YEAST

		Amount		
		Gm.	Teaspoonful	
Powder	Abbott	7	1 1/2	1.0
	Harris...	5	1 1/2	0.45
	Mead ..	7	1 1/2	1.0
	Squibb..	10	1 1/2	0.45
	Vegex (green).	9	1 1/2	0.0
	" (red)..	9	1 1/2	0.0
Paste (autolyzed) Vegex.		12	1 1/2	1.0
Tablets	Mead. ..		1 1/2	1.0
	Squibb		1 1/2	0.0

The many varieties of mixtures containing vitamins will not be discussed. Although various syrups are to be had, they are not used because they do not contain the unknown ingredients of the yeast in negligible amounts. Prices of powdered yeast are 2 to 6 cents per dose, and of Vegex from 1 to 2 cents per dose. Patients without diarrhea or polyuria may be given in addition to the high vitamin diet, a dose containing thiamine three times daily, beaten up in water, tomato juice or broth. Patients with diarrhea or malabsorption need the same dose five or six times daily.

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For patients with severe neuropsychiatric disorders due to B vitamin deficiencies Jolliffe (1941) has advised 2 to 3 cc. daily. This costs about 16 to 25 cents per dose.

Some of these extracts are padded with extra crystalline vitamins, as:

B Complex Parenteral (Lederle) for intramuscular injection, a liver concentrate containing,

Thiamine	3,000	micrograms	per	gm.
Riboflavin	500	"	"	"
Niacinamide	10,000	"	"	"
Pantothenate	1,680	"	"	"
Pyridoxine	450	"	"	"

This costs about 25 cents per gm.

There are many such products on the market. Note should be made of their contents. Aside from the discomfort and cost of intramuscular injections and the risk of producing sensitivities, they are relatively expensive sources of the B vitamins and these are often not present in the best proportions. Moreover, relatively large doses must be given parenterally, because the water-soluble vitamins are rapidly excreted even in the presence of tissue need. Except for patients so ill that they cannot absorb and utilize preparations given orally, parenteral use is not advised.

3. *Yeast*.—A variety of *Saccharomyces cerevisiae* used by brewers is grown on a special medium, is killed, dried and powdered. It is marketed as powdered brewer's yeast. It is also compressed into tablets and autolyzed with salt to form a paste marketed as "Marmite" or "Vegex." Both these forms have been widely used for animals and man by the most experienced and critical students of deficiency diseases and provide today the soundest basis for the treatment of deficiencies of the B vitamins. They contain all of the known B nutrients, namely, thiamine, riboflavin, niacin (nicotinic acid), pyridoxine, pantothenic acid, inositol, biotin, para-aminobenzoic acid, choline, as well as others not yet isolated. The powdered and the paste forms are usually better tolerated than the compressed tablets. As 16 or 17 of the tablets must be taken to supply 1 mg. (1000 micrograms) of thiamine, discomfort is often the result. Moreover, suspension in fluid seems to favor absorption.

In Table 8 are listed several of the well known brands of brewer's yeast, with the amounts needed to supply 1 mg. of thiamine. The green label Vegex powder is very cheap but has a strong hop flavor which has been eliminated in the red label product. The Harris powder has more thiamine per unit of bulk than the others, and is almost tasteless. Mead's contains more riboflavin and is marketed in convenient wide-mouthed 6-ounce bottles. Squibb's is slightly flavored and more granular. The Vegex paste tastes like meat extract and because of its high flavor and salt content must be accurately measured (1 scant teaspoonful) and well mixed with soups or tomato juice.

TABLE 8
BREWER'S YEASTS

		Amount		Thiamine, Mg.	Riboflavin, Mg.
		Gm.	Teaspoonfuls		
<i>Powder</i>	Abbott . .	7	3½	1.0	1.0
	Harris.....	5	2½	1.0	0.45
	Mead....	7	3½	1.0	1.0
	Squibb..	10	5	1.0	0.45
	Vegex (green).	9	4½	1.0	0.9
	" (red)...	9	4½	1.0	0.9
<i>Paste (autolyzed) Vegex.</i>		12	2	1.0	1.0
<i>Tablets</i>	Mead....	17 tablets		1.0	1.0
	Squibb..	16 "		1.0	0.5

The many varieties of mixtures containing crystalline vitamins will not be discussed. Although attractive capsules and syrups are to be had, they are not advised because they do not contain the unknown ingredients of the yeast—or only in negligible amounts. Prices of powdered yeast vary from 2 to 6 cents per dose, and of Vegex from 5 to 7 cents per dose. Patients without diarrhea or polyuria may be given, in addition to the high vitamin diet, a dose containing 1 mg. of thiamine three times daily, beaten up in water, milk, tomato juice or broth. Patients with diarrhea or marked polyuria may need the same dose five or six times daily.

SPECIFIC B VITAMINS.—Only for patients with clinical syndromes referable to specific vitamin deficits, are the specific B vitamins advised. In such cases they are always given in addition to the whole complex as noted previously.

DOSAGES

Thiamine

To saturate, 1 mg. orally, five times daily for five days.

If diarrhea or polyuria, liver disease or alcoholism is present, 5 to 10 mg. by mouth, five times daily.

If an acidity or vomiting is present, 1 to 2 mg. intramuscularly two to five times daily.

In collapse or heart failure, 100 mg. intravenously, and 300 mg. intramuscularly, followed by decreasing intramuscular doses every three to six hours for two to three days, and then by 10 mg. daily by mouth during convalescence.

Tablets for oral use cost about 1 cent per milligram. Preparations for parenteral use cost more.

Riboflavin

One to 5 mg. orally, five times daily (Sydenstricker, 1941).

If diarrhea or polyuria is present, five to ten times this amount.

Capsules for oral use cost about 2 cents per milligram.

Parenteral injection is rarely needed, but may be given.

Riboflavin is light sensitive.

Niacinamide

Five to 10 to 50 mg. orally, five times daily.

If severe encephalopathy is present, 100 to 200 mg. parenterally.

It costs about 0.03 to 0.05 cents per milligram.

These large doses are advised for short periods of time for patients whose symptoms are severe, because prompt replenishment is imperative and waste is of minor economic importance (Jolliffe, 1941; Youmans, 1941). These B vitamins are usually easily absorbed, but are easily destroyed in the gut if gastric acidity is low, either spontaneously or owing to alkaline therapy. They are also readily excreted in urine, sweat and diarrheal stools. In all these circumstances, repeated doses and amounts of five to ten times the normal needs are necessary (Spies et al., 1940; Sydenstricker, 1941).

OTHER B VITAMINS.—At present, if thiamine, riboflavin and niacin are present in sufficient amounts in natural foods, the other nutrients of the B complex may be considered adequate.

Ascorbic Acid

As with the B vitamins, if the dietary history discloses a lack which is only slight, dietary adjustment alone can easily rectify this. Two or three times the usual amount can be comfortably taken through proper selection of fruits and vegetables. If food fads are a problem in the case, or if other conditions interfere with the use or increase the needs, ascorbic acid is best given by mouth. A tablet of 25, 50 or 100 mg. may be given three to five times daily according to the urgency of need. It costs 0.02 to 0.03 cents per mg. It is rarely necessary to give it parenterally. It can be given intravenously, but its acid reaction precludes subcutaneous use. Like the other water-soluble vitamins it is easily destroyed in the gut if gastric acidity is low or alkaline therapy is given. It is rapidly excreted in urine, sweat and diarrheal stools, and in such circumstances frequent doses of five to ten times the usual amounts are advised (Crandon et al., 1940; Field et al., 1940; Ingalls et al., 1937; Lanman et al., 1937).

Special attention is called to the washing out of the water-soluble vitamins by parenteral fluid therapy as well as to the extra need for them in the metabolism of the dextrose given. Incorporation of thiamine in the injection mixture is advised (Holman, 1940).

If the patient is able to take and utilize a proper diet and can be taught to do so, these extra vitamins need be given for only one to three weeks, according to the duration and severity of the past deficit. There seems to be no danger from large doses, but it must be remembered that long-continued imbalance between the different members of the B vitamins may lead to relative deficits which will upset metabolic processes.

THE FAT-SOLUBLE VITAMINS

Vitamins A and D

Vitamins A and D are the only vitamins which are advised as a general routine. To *all infants* in temperate or cold climates during the first three years of life they should be given. This is because man does not usually obtain vitamin D from his food but from activation of dehydrocholesterol in the

skin by the ultraviolet rays of sunlight. During infancy this is rarely provided in such climates. Moreover, the vitamin A of the usual commercial cow's milk is not sufficient for the needs of growth. Therefore, these vitamins are routinely supplied, not in natural foods, but by medicinal preparations either as U.S.P. cod liver oil or partly concentrated or greatly concentrated fish liver oils; *e.g.*:

	Vitamin A, I.U.	Vitamin D, I.U.
Cod liver oil, U.S.P., 1 to 2 teaspoonfuls	4000 to 8000	400 to 800
Cod liver oil (Squibb), $\frac{1}{2}$ to 1 teaspoonful .	4000 to 8000	600 to 1200
Navitol (Squibb), 2 to 4 drops	2000 to 4000	400 to 800
Percomorph oil (Mead), 2 to 4 drops	2000 to 4000	400 to 800

These doses are put directly into the infant's mouth rather than into food, where the oil adheres largely to glass or nipple. The cost of such prophylactic doses varies from 0.3 to 1.2 cents daily, the concentrates being usually less expensive per unit of vitamin D than the simple fish liver oils, which, of course, have other nutritive value in the fat. For the cure of *rickets*, three to five times these doses are given.

For older patients, dietary deficits of vitamin A can be easily corrected by foods alone. since there are many acceptable ones rich in this vitamin, notably apricots, carrots, eggs, all green leaves, liver, peppers and squash. If there are anatomical lesions, the vitamin should be given in medicinal preparation. As large doses will be given for long periods of time. for especially slow to heal are the skin (Frazier, 1936) and eye lesions (Kruse, 1941) of vitamin A deficiency, it is best to choose one of the fish liver oils less rich in vitamin D as:

	Vitamin A, I.U.	Vitamin D, I.U.
Halibut liver oil, plain (Abbott), 10 drops .	10,000	180
Halibut liver oil, plain (Mead), 10 drops	9,200	160

These vitamins are stored in the body and the dose of 10 to 20 drops may be given at once on a cube of bread.

To patients with sprue, celiac disease, prolonged diarrhea and cancer, it may be necessary to give vitamin A parenterally, since both bile and pancreatic lipase are necessary for

absorption (Blackfan and Wolbach, 1933; Irvin et al., 1941). Products for such use are expensive.

In preparation for operation (Holman, 1940) and during convalescence or prolonged confinement indoors, as well as during pregnancy and lactation, the usual preparations prescribed for infants, with more vitamin D, are best; e.g.:

	Vitamin A, I.U.	Vitamin D, I.U.
Navitol (Squibb), 10 drops 10,000	2,000
Percomorph oil (Mead), 10 drops	. 12,000	1,700

or if the taste is not tolerated, one capsule of either daily, which is only slightly more expensive. Viosterols and "Drisdol" (Winthrop) contain only vitamin D and should be chosen only when it is definitely desired to exclude vitamin A.

Capsules containing vitamin A and D incorporated with other vitamins are not advised since regulation of dosage cannot be properly managed.

Vitamin K

The therapeutic use of this vitamin has been recently reviewed in these pages by Lozner and Kark (1941).

SCHEDULE FOR VITAMIN THERAPY IN SPECIAL CONDITIONS

Attention to dietary adequacy of vitamins is indicated for almost all patients. In treatment of mild deficiencies, in preparation for operation, in early vomiting of pregnancy, during convalescence or prolonged illness and for patients whose diets must be restricted the following daily regimen is suggested:

- 6 A.M. Citrus or tomato juice, 100 cc. (3½ ounces).
- 8 A.M. Milk, 200 cc. (7 ounces) plus yeast powder, 1 tablespoonful.
- 10 A.M. Broth, 200 cc. (7 ounces) plus VegeX, 1 scant teaspoonful.
- 12 noon Citrus or tomato juice, 100 cc. (3½ ounces).
- 2 P.M. Milk, 200 cc. (7 ounces) with yeast power, 1 tablespoonful.
- 4 P.M. Broth, 200 cc. (7 ounces) with VegeX, 1 teaspoonful.
- 6 P.M. Citrus or tomato juice, 100 cc. (3½ ounces).
- 8 P.M. Milk, 200 cc. (7 ounces) with yeast, 1 tablespoonful.

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To patients with sprue, celiac disease, prolonged diarrhea and cancer, it may be necessary to give vitamin A parenterally, since both bile and pancreatic lipase are necessary for

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This will provide 1300 cc. of water. Extra water and salt may be allowed as desired. Ascorbic acid (25 mg.) is given with each feeding (total for day, 200 mg.) and vitamin A (10,000 units) and vitamin D (1000 units) are given in one dose. Vitamin K is administered as indicated by the prothrombin clotting time. Other foods are given as indicated.

COMMENT

Vitamins are nutrients, not drugs. If enough of them for current use are supplied in the diet, no effect can be expected by giving more of them. If extra sources are needed, it is evidence of dietary lack. In spite of the dramatic effects of severe or long-standing vitamin deficiencies, vitamins should not be thought of as "anti this" or "anti that" but as ingredients of the metabolic mixture essential for health.

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PRESENT STATUS OF SULFONAMIDE THERAPY*

CHARLES H. RAMMELKAMP, M.D.†

THERE is no longer any doubt that the sulfonamide drugs exhibit a dramatic curative effect in a number of infections. This is especially true in lobar pneumonia, epidemic meningitis, and gonorrhea. In other infections, such as staphylococcal sepsis and certain urinary tract infections, the response following sulfonamide therapy is definite but not dramatic. There is a third group of diseases, including typhoid fever and anthrax, in which sulfonamide therapy is of doubtful value. Further, numerous sulfonamide drugs are now available, so that one is frequently confronted with several questions: (1) will the infection respond to sulfonamide therapy; (2) what is the drug of choice from the standpoint of both effectiveness and lack of toxicity; and, finally, (3) how much of the drug should be administered? It is the purpose of this clinic to outline briefly the answers to these questions.

TOXICITY

Before discussing the various infections it is well to review some of the more frequent toxic manifestations of the sulfonamide drugs. These are best illustrated in tabular form. From the accompanying tabulation it is at once apparent that undesirable side reactions such as cyanosis, fever, rashes, anemia and jaundice are especially likely to follow *sulfanilamide* therapy. The most serious reactions following administration of sulfanilamide are acute hemolytic anemia, which usually occurs during the first few days of therapy, hepatic damage and leukopenia. *Sulfapyridine* causes less toxic reactions but

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somewhat less important role in determining the drug of choice. These factors, then, are taken into consideration in the discussion of the sulfonamide drugs recommended for use in the treatment of the different infections.

STREPTOCOCCAL INFECTIONS

Infections caused by the hemolytic streptococcus account for a large percentage of illness in both civilian and army life. In treating streptococcal infections one must consider both the *toxic* and *septic* phases of the disease. That sulfonamide therapy has no effect on the toxic manifestations has been demonstrated both by its failure to neutralize streptococcal toxin *in vitro* and by its action in the toxic phase of scarlet fever. The toxic manifestations are best treated with antitoxin or convalescent serum. The septic phase is favorably affected by sulfonamide therapy and also by immunotransfusions.

The value of *sulfanilamide* therapy in streptococcal infections is now well established. When 8 to 10 gm. is administered daily in divided doses, the necessary concentration of 7 to 15 mg. per 100 cc. is usually obtained in the blood. Although clinical experience with *sulfapyridine* and *sulfathiazole* is somewhat limited, both drugs exhibit a beneficial effect in streptococcal infections.

The drug of choice in streptococcal infections is sulfadiazine. This has been determined both by comparative tests in the laboratory and by the results obtained in the treatment of experimental and clinical infections. The usual dosage is 4 gm. followed by 1 gm. every four hours. In order to obtain maximal action a concentration of from 6 to 12 mg. of sulfadiazine per 100 cc. should be maintained in the blood.

Bacteremia

Invasion of the blood stream occurs not infrequently during the course of hemolytic streptococcus infections of the skin, respiratory passages and uterus. When such an event takes place, 75 per cent of all patients succumb to the infection if adequate chemotherapy is not employed. *Sulfadiazine* should be administered in full dosage, maintaining a concen-

TABULATION
TOXIC MANIFESTATIONS OF THE SULFONAMIDE DRUGS

	Sulfa- nilamide	Sulfa- pyridine	Sulfa- thiazole	Sulfa- diazine
Nausea and vomiting....	++	++++	+++	+
Fever.....	+++	+++	++++	+
Rash.....	+++	++	+++	+
Anemia.....	++++	++	+	+
Jaundice.....	++	+	=	?
Leukopenia.....	+++	+++	+	+
Anuria or oliguria.....	-	+++	+++	++

nausea and vomiting are common, and hematuria and oliguria may be serious. *Sulfathiazole* is somewhat less toxic than sulfanilamide or sulfapyridine, but the incidence of drug fever and rashes following the use of sulfathiazole not infrequently confuses the clinical course of an infection. *Sulfadiazine*, which was introduced recently, is the least toxic of the four drugs. *Renal complications* following sulfapyridine, sulfathiazole and sulfadiazine occur not infrequently, and it is therefore important to stress the fact that the majority of these complications can be prevented if the urinary output is kept between 1200 and 1800 cc. daily.

CHOICE OF SULFONAMIDE

The etiologic agent is of utmost importance in determining which sulfonamide drug is to be administered. It is because of this fact, then, that cultures from the suspected focus (ear, throat, sputum, blood, urine, stool, or spinal fluid) should be taken before the institution of chemotherapy. Fortunately, in the majority of infections the etiologic agent may be determined from the clinical picture so that the proper drug may be administered at once. In those infections in which the causative organism is not known, sulfadiazine should be administered until the results of the cultures have been obtained. *Sulfadiazine is the drug of choice* in such instances since it is effective against the largest number of the bacterial species.

In addition to the etiologic agent, the location of the infection and the toxic effects of the sulfonamide drug play a

somewhat less important role in determining the drug of choice. These factors, then, are taken into consideration in the discussion of the sulfonamide drugs recommended for use in the treatment of the different infections.

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tration of at least 10 mg. per 100 cc. in the blood stream. Treatment should be continued for at least one week after the first negative blood culture and return of the temperature to normal. If available, immunotransfusions are also of benefit in these infections.

Scarlet Fever

Considerable experience with *sulfanilamide* therapy in scarlet fever has demonstrated that it decreases the number of complications. The routine administration of *sulfanilamide* to patients with mild cases of scarlet fever is not recommended because of the high incidence of toxic reactions to the drug.

Sulfadiazine, which is considerably less toxic than *sulfanilamide* and at the same time more active against the streptococcus, is the drug of choice. It should be given in full dosage. It must be emphasized, however, that the administration of convalescent serum or of 10,000 units of antitoxin is indicated in those patients with extensive rash, high fever, or delirium since chemotherapy does not affect these toxic manifestations of the disease.

Erysipelas

The early recognition of erysipelas is important since the administration of *sulfadiazine* or *sulfanilamide* during the first three or four days of illness results in dramatic improvement. *Sulfadiazine* is to be preferred and therapy should be continued for at least one week after the temperature returns to normal.

Meningitis

Before the advent of chemotherapy, 95 per cent of patients with hemolytic streptococcus meningitis died. The administration of *sulfanilamide* in large amounts has lowered the mortality rate to 25-35 per cent, and it seems likely that *sulfadiazine* therapy will prove even more effective. The majority of these infections are secondary to otitis media and acute mastoiditis so that after the institution of *sulfadiazine* therapy the local lesion should be drained. The drug should be administered in sufficient quantities to produce a concentration

in the blood and spinal fluid of 10 to 15 and 8 to 12 mg. per 100 cc. respectively. Drug therapy is continued for ten to fourteen days after the spinal fluid has become sterile. In addition, transfusions are indicated if anemia exists.

Puerperal Sepsis

The beneficial effect of *sulfanilamide* administration in puerperal infections was demonstrated soon after this drug was introduced to the medical profession. Organisms other than hemolytic streptococci may be associated with puerperal infections and for this reason *sulfadiazine* is to be preferred to sulfanilamide.

Pneumonia and Empyema

Hemolytic streptococcus pneumonia occurs most frequently after influenza or measles. Therapy with *sulfanilamide* and *sulfapyridine* has reduced the fatality rate in both pneumonia and empyema. In general, empyema requires surgical drainage although in a few instances the combination of oral chemotherapy and multiple aspirations results in recovery. Again *sulfadiazine* is recommended as the drug of choice in these infections.

Infections of the Ear, Nose and Throat

Sulfonamide therapy has proved of value in the therapy of hemolytic streptococcus infections of the upper respiratory system and accessory sinuses. *Sulfanilamide* therapy has decreased the incidence of mastoiditis in patients with otitis media. In view of the fact that the infecting organism in middle ear and nasal sinus infections is frequently the pneumococcus or staphylococcus, it appears likely that *sulfadiazine* is the drug of choice in the therapy of these infections, at least until the cultures of the involved area identify the infecting organism. In any event, acute otitis media should be treated with *sulfadiazine* or *sulfanilamide* until acute symptoms have subsided. In severe infections the mastoid cavity should also be examined by x-ray since destruction of the mastoid cells is not infrequently delayed by sulfonamide therapy. Once the cells are destroyed, operative interference

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ing sulfathiazole. Sulfadiazine exhibits a definite antibacterial effect when high concentrations are obtained in the blood. Sulfathiazole concentrations should be maintained at 3 to 6 mg. per 100 cc., and sulfadiazine at 8 to 15 mg. per 100 cc. An initial dose of 4 gm. followed by 1 gm. every four hours of either sulfathiazole or sulfadiazine is usually sufficient. Occasionally 1.5 gm. must be administered every four hours.

Bacteremia

Once the diagnosis of *Staphylococcus aureus* bacteremia is established, sulfathiazole should be administered in full dosage. Frequent determinations of the concentration of the drug in the blood are required so that the desired level of 3 to 6 mg. per 100 cc. is maintained. In addition to chemotherapy, 50,000 to 100,000 units of *staphylococcal antitoxin* (globulin-modified) are given intravenously in those patients showing toxic manifestations of the disease. *Transfusions* of whole blood are indicated in patients with anemia.

The *focus of infection should be drained* when it becomes well localized. The failure of the temperature to return to normal or the presence of positive blood cultures after surgical drainage usually indicates further abscess formation and such collections of pus must be drained. It is wise to continue chemotherapy for at least two weeks after all signs of infection have subsided.

By means of the procedures outlined above, it has been possible to reduce the mortality rate from 80 per cent to 35 per cent.

Osteomyelitis

In acute osteomyelitis the administration of *sulfathiazole* is indicated. Adequate doses of this drug should prevent the hematogenous spread of the infection, and, in addition, may limit the local infection of the bone. There is some indication that destruction of the bone is retarded, so that repeated x-rays are often necessary to demonstrate the changes in the bone. Although there is evidence that the local lesion may heal with chemotherapy alone, *surgical drainage* is usually necessary. In chronic osteomyelitis chemotherapy has been of little value.

is necessary. Chemotherapy should be continued for several days after operation.

The routine use of sulfanilamide in streptococcal sore throat, tonsillitis and sinusitis is not advisable. That such therapy has shortened the duration of illness has not been adequately demonstrated. In severe infections *sulfadiazine* or *sulfanilamide* should be administered in adequate dosage. The beneficial effects of a local spray to the involved area are also of doubtful value.

Miscellaneous Infections

Infection of the *pericardial* or *peritoneal cavity* with hemolytic streptococci should be treated with large doses of *sulfadiazine*, maintaining a concentration of 10 to 15 mg. per 100 cc. in the blood. The local application of sulfanilamide powder to *wounds*, *ulcers* or *burned areas* reduces the incidence of subsequent infections. Once the infection has been established, those due to hemolytic streptococci respond satisfactorily to local therapy whereas other types of infecting organisms have been somewhat more resistant.

STAPHYLOCOCCAL INFECTIONS

Infections caused by *Staphylococcus aureus* tend to remain localized and are chronic in nature. Occasionally the defensive mechanisms of the body break down and the organisms gain access to the circulating blood. When this occurs, metastatic abscess formation is the rule. These abscesses are especially likely to occur in the lungs, bones and muscles. Failure to drain the original or the metastatic foci of infection accounts for the majority of fatalities. Sulfonamide therapy is of value because it helps to keep the infection localized and prevents metastatic abscess formation. As a general rule the sulfonamide drugs will not sterilize localized collections of pus, so that *surgical drainage should be established in all cases*.

It is now recognized that sulfanilamide has little effect on staphylococcal infections. From the standpoint of antibacterial effect, *sulfathiazole* is the drug of choice. *Sulfadiazine* is indicated if the patient shows toxic manifestations follow-

ing sulfathiazole. Sulfadiazine exhibits a definite antibacterial effect when high concentrations are obtained in the blood. Sulfathiazole concentrations should be maintained at 3 to 6 mg. per 100 cc., and sulfadiazine at 8 to 15 mg. per 100 cc. An initial dose of 4 gm. followed by 1 gm. every four hours of either sulfathiazole or sulfadiazine is usually sufficient. Occasionally 1.5 gm. must be administered every four hours.

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Pneumonia

Staphylococcal pneumonia occurs most frequently as a complication of influenza. There is a tendency in such infections toward the formation of multiple abscesses and empyema. Either *sulfathiazole* or *sulfadiazine* should be administered in full dosage of 1 gm. every four hours. It is best to continue chemotherapy for at least two weeks after the temperature returns to normal. Administration of these drugs has caused a decrease in the number of fatal infections.

Meningitis and Cavernous Sinus Thrombosis

Several patients with *staphylococcal meningitis* have recovered following chemotherapy. Sulfadiazine is the drug of choice since high concentrations (8 to 12 mg. per 100 cc.) can be obtained in the spinal fluid. Sulfathiazole is beneficial if sulfadiazine cannot be obtained.

In *cavernous sinus thrombosis*, sulfathiazole or sulfadiazine administration is indicated. In addition, heparin is given in amounts sufficient to keep the clotting time between sixty and ninety minutes. In order to be successful, chemotherapy must be continued for several weeks.

Urinary Tract

Sulfathiazole and sulfadiazine are both effective in *pyelocystitis* due to the staphylococcus. Infections which fail to respond after several days of chemotherapy usually are associated with abscesses of the kidney. These abscesses require *surgical drainage* as well as chemotherapy.

Carbuncles, Furuncles, Wounds and Burns

The administration of sulfathiazole or sulfadiazine by mouth to patients with *carbuncles* or *large boils* is indicated primarily to assure that the infection remains localized and thus prevent invasion of the blood stream. Surgical drainage should be established as soon as the lesion is well localized.

The local application of small amounts of sulfanilamide powder or a mixture of sulfanilamide and sulfadiazine or sulfathiazole in the proportion of 3 to 1 is useful in *fresh wounds* or *burns*. Such therapy supplemented by oral sulfathiazole

therapy may prevent staphylococcal infections. Once staphylococcal infection of wounds or burns is established, local applications of the sulfonamide do not sterilize the local lesion.

PNEUMOCOCCAL INFECTIONS

Sulfapyridine, sulfathiazole and sulfadiazine have all been found to possess antibacterial properties against the pneumococcus. From the standpoint of lack of toxicity and a high degree of antibacterial action, *sulfadiazine is the drug of choice.*

Pneumonia

After blood cultures and sputum cultures have been obtained for typing, chemotherapy should be instituted immediately. An initial dose of 4 gm. of sulfadiazine followed by 1 gm. every four hours is usually employed. In the majority of patients clinical improvement is noted within twenty-four to forty-eight hours after the start of chemotherapy. In a few patients type-specific *antisera* must be administered in addition to chemotherapy. A full discussion of the status of sulfonamide therapy in pneumonia is presented elsewhere in these clinics.

Meningitis

Before the introduction of chemotherapy at least 98 per cent of patients with pneumococcal meningitis succumbed to the infection. The fatality rate can be reduced to 70-80 per cent by the daily administration of from 6 to 8 gm. of either sulfadiazine or sulfapyridine. A concentration of the drug of at least 8 mg. per 100 cc. should be maintained in the spinal fluid. Chemotherapy should be continued for at least ten days after the spinal fluid is sterilized. It is, therefore, important to perform frequent lumbar punctures to determine the presence of organisms and the change in the number of leukocytes in the fluid.

In addition to chemotherapy, *type-specific rabbit serum* should be administered intravenously in doses of about 200,000 units.

Peritonitis

A large number of recoveries may be expected when sulfadiazine or sulfathiazole is administered in the usual dose of 6 gm. daily to patients with pneumococcal peritonitis.

MENINGOCOCCAL INFECTIONS

Meningitis and Bacteremia

Before the advent of chemotherapy, from 20 to 90 per cent of all patients with epidemic meningitis died. Therapy with sulfanilamide, sulfapyridine, sulfathiazole, or sulfadiazine has altered the prognosis so that now more than 85 to 90 per cent of all patients recover. At the present time it is impossible to state which drug is most effective in the treatment of this form of meningitis. It would appear that the sulfonamide drug causing the fewest toxic reactions would be the drug of choice, and for this reason *sulfadiazine* is recommended.

After the initial spinal fluid and blood cultures have been taken, 4 gm. of sulfadiazine should be administered followed by 1 gm. every four hours. Spinal punctures are indicated when there are symptoms of increased pressure, for determination of the concentration of the drug in the spinal fluid, and for following the course of the disease. A concentration of sulfadiazine of from 8 to 12 mg. per 100 cc. should be maintained in the spinal fluid. There is no necessity to administer a concentrated solution of the drug intrathecally. If after twenty-four to forty-eight hours there is no response to chemotherapy, antiserum may be administered. Chemotherapy should be continued for at least three to four days after clinical recovery.

ESCHERICHIA COLI, AEROBACTER AEROGENES, PROTEUS VULGARIS AND STREPTOCOCCUS FAECALIS INFECTIONS

Urinary Tract

The coliform organisms are associated with infections of the urinary tract although occasionally they may invade the blood stream or cause peritonitis or meningitis. The order of effectiveness of the sulfonamide drugs against these organ-

isms is: (1) sulfathiazole, (2) sulfadiazine, (3) sulfapyridine, and (4) sulfanilamide. Sulfanilamide and sulfapyridine display little or no effect against *Proteus vulgaris* or *Streptococcus faecalis*.

The majority of the infections of the urinary tract are caused by the colon bacillus, and in these infections the administration of small quantities of sulfathiazole is usually sufficient to control the disease. Sulfathiazole is given in a dose of 0.5 gm. after each meal, and this dosage maintains a concentration of sulfathiazole in the urine of at least 20 mg. per 100 cc. If there is not an immediate response to such chemotherapy, it usually indicates either (1) the presence of some organism other than *Escherichia coli* or *Aerobacter aerogenes* or (2) a complicating factor producing urinary stasis. The most frequent complications include bladder or renal stones, prostatic hypertrophy, hydronephrosis, and diabetes mellitus. When the infection is caused by *Streptococcus faecalis* or *Proteus vulgaris*, 3 to 6 gm. of sulfathiazole or sulfadiazine should be administered daily. If there is stasis of the urine, the obstruction must be removed. In all urinary tract infections fluid should be forced to at least 3000 cc. daily.

GONOCOCCAL INFECTIONS

As the result of laboratory studies the efficacy of the sulfonamide drugs against the gonococcus in various culture media may be graded as follows: (1) sulfathiazole, (2) sulfadiazine, (3) sulfapyridine, (4) sulfanilamide. Clinically all drugs appear to be effective in the treatment of gonorrhea, sulfanilamide administration resulting in bacteriologic cures in 25 to 30 per cent, sulfapyridine in 50 to 55 per cent, and sulfathiazole in 70 to 75 per cent of the cases. The rate of cure following sulfadiazine therapy has not been determined as yet.

Gonorrhea

Dramatic results may be expected in both the male and female with uncomplicated gonococcal urethritis. Sulfathiazole should be administered in doses of 0.5 gm. four times daily for ten days. Sulfadiazine or sulfapyridine may be used

in similar dosage. Sulfanilamide should be given in somewhat larger doses: 1 gm. four times daily for ten to fourteen days. After five days of chemotherapy, especially sulfathiazole therapy, marked symptomatic improvement can be expected. In the few patients who fail to respond to sulfanilamide or sulfapyridine, a satisfactory response may subsequently be obtained by a second course of chemotherapy, especially when sulfathiazole is used. In general, no patient responds to a third course of chemotherapy.

Gonococcal Epididymitis, Salpingitis, Arthritis

The treatment of the complications of gonorrhea is similar to that of the acute infection except that sulfathiazole or sulfapyridine should be given in full dosage of 1 gm. every four hours for a period of about two weeks.

CLOSTRIDIUM WELCHII INFECTIONS (GAS GANGRENE)

In the experimental animal the sulfonamides have been found to be effective in the treatment of gas gangrene. In man, however, the results obtained following the use of sulfanilamide have not been entirely satisfactory. In the experimental animal sulfadiazine and sulfathiazole are both more effective than sulfanilamide. Therapy should consist, then, of full doses of sulfadiazine by mouth, local débridement, implantation of several grams of sulfanilamide locally, and the administration of antitoxin.

INFLUENZAL MENINGITIS

Infections due to the influenza bacillus are confined chiefly to the meninges. In influenzal meningitis it is important to culture the spinal fluid and type the organism since the evidence seems to indicate that specific serum combined with chemotherapy gives the best results. Sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine are all effective. Whichever drug is used, it should be administered in full

dosage and be continued for at least ten days after clinical recovery.

VIRUS INFECTIONS

In general, virus diseases do not respond to chemotherapy with the sulfonamide drugs. There are two exceptions to this statement. *Trachoma* has responded to seven to fourteen days' therapy with either sulfanilamide or sulfapyridine. *Lymphogranuloma venereum* responds to prolonged therapy with sulfanilamide, sulfapyridine and sulfathiazole. When there is involvement of the rectum, sulfaguanidine has also been found to be of value.

CONCLUSIONS

The decision as to which sulfonamide drug should be employed and the amount to be administered is determined primarily by knowledge of the following factors:

1. The relative sensitivity of the infecting organism to the sulfonamide drugs.
2. The toxicity of the various drugs.
3. The location and severity of the infection.

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COMMON LABORATORY AIDS TO DIAGNOSIS AND TREATMENT*

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THE application of chemical, physical and physiological methods of investigation to clinical medicine has resulted in tremendous advances in our understanding of human disease. Many of these procedures are so complex that their use is still restricted to research laboratories. Fortunately, however, those procedures essential for the adequate diagnosis and therapy of the more common diseases now have been simplified and are easily performed in any clinical laboratory. Although laboratory studies will never supplant skillful and painstaking clinical history-taking and physical examination, they do yield information which is indispensable for the proper diagnosis and management of patients, and the performance of a test so simple as the determination of urinary specific gravity may save many hours of time and indicate life-saving therapy.

Only a few of the more practical laboratory procedures can be discussed in this paper; complete discussions of available diagnostic procedures will be found in the classic treatise of Peters and Van Slyke,¹ in the excellent book of Bodansky and Bodansky,² and in the recent reviews of Myers and Muntwyler^{3, 4} and Cantarow.⁵

VITAMIN DEFICIENCIES

The vague symptoms of borderline vitamin deficiency and the frequency with which these symptoms simulate neurasthenia and psychoneurosis make objective laboratory evidence of the state of vitamin nutrition particularly valuable

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clinical significance. Normal individuals excrete more than 100 micrograms of thiamine in twenty-four hours, and an excretion of 70 micrograms or less in this period of time is almost certain evidence of thiamine deficiency.¹⁶

Tolerance tests are extremely useful in detecting the less severe degrees of deficiency, and are performed relatively easily.¹⁷ The subject is fed 5 mg. of thiamine, and the urinary excretion of the vitamin is followed at hourly intervals. If deficiency exists, the total excretion will be very small, and the maximum urinary concentration reached will be only one-fourth to one-fifth that commonly observed in normal controls.

Thiamine deficiency is commonly encountered in diseases associated with poor nutrition, especially ulcerative colitis, carcinoma, thyrotoxicosis and cirrhosis.

RIBOFLAVIN (VITAMIN B₂).—The technics for the quantitative estimation of riboflavin are still fairly complex, although following suitable extraction from the blood or urine its property of fluorescing in ultraviolet light allows reasonably accurate determinations to be made in the fluorophotometer.¹⁸

The blood of normal subjects contains between 35 and 45 micrograms of riboflavin per 100 cc. Identical values have been reported in patients with frank riboflavin deficiency,¹⁹ indicating the futility of attempting to estimate riboflavin nutrition on the basis of blood levels. In contrast to the unreliability of the blood levels, the urinary levels closely parallel the dietary intake of riboflavin, and restriction of riboflavin in the diet to 1 or 2 mg. per day decreases the urinary excretion from the normal value of 500 to 800 micrograms per day to a level of 50 to 150 micrograms per day.²⁰ A tolerance test in which 5 mg. of riboflavin is fed in addition to the diet gives promise of being very helpful. Most of the surplus amount is normally excreted immediately in the urine, but in subjects with riboflavin deficiency there is only slight increase in urinary output.

Practically the difficulties involved in the chemical determination of riboflavin limit the general use of this test, but it is now recognized that riboflavin deficiency is almost al-

to the practicing physician. Chemical determinations of the actual levels of vitamins in the blood can be made, but in general are not as useful an index of the adequacy of vitamin supplies in the body as are determinations of the amount excreted in the urine. When tissue stores of vitamins are adequate, considerable quantities usually appear in the urine, while in deficiency states urinary excretion is greatly diminished or actually ceases.

Vitamin A

Direct quantitative measurement of vitamin A in the blood serum is easily performed and depends upon the development of a blue color when the vitamin reacts with *antimony trichloride*, the intensity of the color varying directly with the concentration of the vitamin.⁶ This procedure is preferable to tests of dark adaptation. The range in normal human subjects is between 60 and 190 U.S.P. units per 100 cc. of plasma.⁷ In cases of xerophthalmia only a trace of vitamin A could be detected in the plasma⁸ and the levels were markedly lowered in acute infections,⁹ in cancer of the gastro-intestinal tract,¹⁰ cirrhosis of the liver,¹¹ and sprue.¹² Increased amounts are found in cases of lipemia, e.g., in nephrosis, hypothyroidism and xanthomatosis.¹³

The so-called *vitamin A tolerance test* has been extensively used as an indicator of fat absorption. A specified amount of vitamin A is administered by mouth and the level of the material in the blood plasma is subsequently determined at varying intervals. Normal individuals show a marked increase in the vitamin A levels of the blood, but patients with sprue show little or no increase,¹² indicating a fundamental defect in lipid metabolism in this disease.

Vitamin B Complex

THIAMINE (VITAMIN B₁).—Estimations of thiamine depend upon the oxidation of the vitamin to *thiochrome*, and subsequent determination of the intensity of fluorescence of this material in ultraviolet light.^{14, 15} Estimates of the state of thiamine nutrition are based principally on the amounts of the material excreted in the urine, since blood levels have little

excreted in the urine. Excretion of less than 13 mg. of ascorbic acid in twenty-four hours indicates probable vitamin C deficiency.²⁷ Normal individuals excrete approximately 40 mg. per day.²⁸ The saturation of the body with vitamin C also can be determined by feeding a test dose of vitamin C (5 mg. per pound of body weight) and determining the amount excreted in the urine during the ensuing twenty-four hours. Normal subjects excrete more than half the test dose while deficient individuals excrete considerably less than this amount.²⁷

Vitamin C deficiency is in all probability much more common than is usually appreciated. In addition to the role played by low dietary intake of ascorbic acid, acute infections,²⁹ chronic illnesses³⁰ and pregnancy contribute to the production of this deficiency by increasing the metabolic needs for the vitamin. Subclinical degrees of deficiency are occasionally responsible for slow healing of surgical incisions and other wounds.³¹

TABLE 1
BLOOD AND URINE VITAMIN LEVELS

	Normal Blood Level	Normal Daily Urinary Excretion	Commonly Decreased in
Vitamin A.	60-100 international units per 100 cc. (plasma)	Negligible	Sprue, celiac disease, cirrhosis, cancer of gastrointestinal tract, xerophthalmia, pneumonia, hypothyroidism.
Thiamine (B ₁)	3.5-4.2 micrograms per 100 cc. (whole blood).	80-300 micrograms	Nutritional deficiency—beriberi, cirrhosis, carcinoma, ulcerative colitis.
Riboflavin (B ₂)	35-45 micrograms per 100 cc. (whole blood).	500-800 micrograms	Ophthalmologic disorders. Dermatological diseases.
Nicotinic Acid	10-15 micrograms per cc. of red cells.	3-10 milligrams	Pellagra. General nutritional deficiency.
Vitamin C.	0.5-2.0 milligrams per 100 cc. (plasma).	15-50 milligrams	Scurvy, acute infections, rheumatic fever, pregnancy.
Vitamin K.	(Prothrombin time 90-110 per cent).	Negligible	Hemorrhagic disease of newborn. Biliary obstruction, ulcerative colitis, acute hepatitis.

Vitamin K

This vitamin has been synthesized in several laboratories, and its chemical structure is well known, but clinical tests

ways associated with thiamine or nicotinic acid deficiency, and definite chemical evidence of either of these deficiency states is fairly readily obtained. Foodstuffs containing abundant supplies of either thiamine or nicotinic acid also contain adequate quantities of riboflavin.

NICOTINIC ACID.—Nicotinic acid reacts with paramethylaminophenol sulfate and cyanogen bromide in aqueous solution of potassium dihydrogen phosphate to produce a stable, clear yellow color. The color developed is proportional to the concentration of nicotinic acid, and allows colorimetric determination of the content of nicotinic acid in urine,^{21, 22} a determination which is fairly simple and of considerable value as an indication of the state of nicotinic acid nutrition. Normal individuals excrete 3 to 10 mg. of nicotinic acid or its derivatives in twenty-four hours, while patients with pellagra show extremely low excretion. Nicotinic acid *tolerance tests* are of considerable usefulness in determining the ability of the body to assimilate the vitamin. When 150 to 300 mg. of nicotinic acid are administered by mouth, normal individuals excrete 20 per cent of the vitamin in the urine within three hours, although patients with deficiency excrete only 3 per cent.

Blood levels of nicotinic acid are of little diagnostic value, since normal and deficient subjects do not show significant variations.²³

Vitamin C

Chemical procedures for the determination of vitamin C depend upon the reducing power of the double bond in the molecule of ascorbic acid. Protein-free preparations of blood plasma or urine are allowed to react with a colored indicator (Tillmans' reagent: 2, 6 dichlorophenolindophenol), and the reducing power of the ascorbic acid decolorizes the reagent in proportion to the concentration of the vitamin.^{24, 25}

The adequacy of vitamin C nutrition may be indicated by repeated determinations of its concentration in the blood, but blood levels vary markedly in normal individuals, and such determinations frequently prove confusing.²⁶ A more reliable index of the extent of vitamin C saturation is the amount

ciency of the kidneys is expressed as the volume of blood "cleared" of some constituent (e.g., urea, creatinine, or inulin) per minute. The sensitivity of the clearance tests is indicated by the fact that they may show a decrease in renal function amounting to 30 per cent when all other procedures show "normal function."³⁴ Although the inulin clearance is diodrast clearance are more accurate, the urea clearance is quite satisfactory for general clinical use, and the simplicity of its technic allows its use in any laboratory equipped to perform ordinary urea determinations.³⁵

The urea clearance test is based upon the fact that if the excretion of urea per minute in the urine is determined, and if the concentration of urea per cubic centimeter of blood is known, then the amount of blood cleared of urea per minute can be found by dividing the output of urea by the concentration of urea in the blood according to the following formula:

$$\text{Urea clearance} \quad \frac{\text{Mg. of urea excreted per minute}}{\text{Mg. urea per cc. of blood}}$$

$$\left(\begin{array}{l} \text{cc. of blood cleared} \\ \text{per minute} \end{array} \right) =$$

Practically the test is performed in fasting subjects who are preferably kept in bed during the procedure.

1. The subject is given two glasses of water, one at the beginning of the test and the other an hour later. He empties his bladder after drinking the first glass of water and the exact time is noted.

2. After approximately one hour the exact time is again noted, the patient voids and the specimen is saved.

3. The time is again noted and a sample of venous blood is drawn for determination of urea concentration.

4. At the end of the second hour the time is noted exactly and the patient again voids. The sample is saved for analysis.

5. The volume of each urine sample is carefully measured and the volume excreted per minute is calculated. The urea concentration of each sample is determined.

6. Calculations:

- (a) If the volume of urine excreted per minute is more than 2 cc., the "maximum clearance" (C_m) is calculated from the formula:

for the adequacy of the body's supply are indirect and depend upon the utilization of the vitamin for the formation of prothrombin. Interference with the supply of vitamin K (e.g., in hemorrhagic disease of the newborn), disturbance of its absorption (biliary obstruction, ulcerative colitis) or its improper utilization by the liver for prothrombin formation (acute hepatitis) results in a decrease in the amount of prothrombin in the blood plasma.

Decreased prothrombin can be detected clinically by determining the so-called *prothrombin time*, which is based on the clotting time of oxalated plasma after adding an excess of thromboplastin and a fixed amount of calcium.^{32, 33} Actually 80 per cent of the prothrombin can be lost before the coagulation time is appreciably prolonged, and clinically it has been found that serious hemorrhage does not occur until the prothrombin sinks below 20 per cent.

RENAL FUNCTION

In addition to the indispensable and universally used routine examination of the urine for color, reaction, specific gravity, protein and sugar content and the presence of leukocytes, erythrocytes and casts, there are three easily performed and extremely informative procedures which should be applied to the study of any patient suspected of renal abnormality. The ability of the kidneys to concentrate and dilute the urine is indicated by the concentration and dilution tests; the excretory capacity of the tubular epithelium is shown by the phenolsulfonphthalein dye excretion; and the ability of the kidney to remove waste from the blood is accurately indicated by the urea clearance. Each procedure tests one or more of the functional activities of the kidney, and serves to detect abnormalities before there is actual accumulation of waste products in the blood. They are of greatest value in following the progress of the disease process and in evaluating the effectiveness of specific therapy.

Urea Clearance

The most sensitive tests of renal functional efficiency are the so-called "clearance tests," in which the functional effi-

ciency of the kidneys is expressed as the volume of blood "cleared" of some constituent (*e.g.*, urea, creatinine, or inulin) per minute. The sensitivity of the clearance tests is indicated by the fact that they may show a decrease in renal function amounting to 30 per cent when all other procedures show "normal function."³⁴ Although the inulin clearance is diodrast clearance are more accurate, the urea clearance is quite satisfactory for general clinical use, and the simplicity of its technic allows its use in any laboratory equipped to perform ordinary urea determinations.³⁵

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$$\text{Urea clearance} \quad \text{Mg. of urea excreted per minute} \\ \left(\begin{array}{l} \text{cc. of blood cleared} \\ \text{per minute} \end{array} \right) = \frac{\hspace{1.5cm}}{\text{Mg. urea per cc. of blood}}$$

Practically the test is performed in fasting subjects who are preferably kept in bed during the procedure.

1. The subject is given two glasses of water, one at the beginning of the test and the other an hour later. He empties his bladder after drinking the first glass of water and the exact time is noted.
2. After approximately one hour the exact time is again noted, the patient voids and the specimen is saved.
3. The time is again noted and a sample of venous blood is drawn for determination of urea concentration.
4. At the end of the second hour the time is noted exactly and the patient again voids. The sample is saved for analysis.
5. The volume of each urine sample is carefully measured and the volume excreted per minute is calculated. The urea concentration of each sample is determined.
6. Calculations:

(a) If the volume of urine excreted per minute is more than 2 cc., the "maximum clearance" (C_m) is calculated from the formula:

$$C_m = \frac{UV}{B}$$

where U = mg. of urea nitrogen in 100 cc. of urine.
 V = volume of urine in cc. per minute.
 B = mg. of urea nitrogen in 100 cc. of blood.

The percentage of normal function can be calculated using the simplified formula:

$$\text{Percentage of normal function} = 1.26 \frac{UV}{B}$$

(b) If the amount of urine excreted is less than 2 cc. per minute, the "standard clearance" (C_s) is calculated from the formula:

$$C_s = \frac{U\sqrt{V}}{B}$$

where \sqrt{V} is the square root of the volume of urine excreted per minute.

The percentage of normal function is calculated from the simplified formula:

$$\text{Percentage of normal function} = 1.86 \frac{U\sqrt{V}}{B}$$

Normally the maximum clearance varies between 60 and 100 cc. per minute, with an average of approximately 75 cc., while the standard clearance varies between 40 and 65 cc. with an average value of 54 cc. Glomerulonephritis produces marked decrease in the urea clearance because of the damage produced to the glomeruli, and the consequent decrease in the facility of glomerular filtration. Nephrosclerosis is also associated with a pronounced decrease in urea clearance because the vascular changes reduce the total blood flow to the kidney.

Concentration and Dilution Tests

The ability of the kidneys to concentrate the urine is one of the first functions to show abnormality in renal disease³⁵ and when properly performed the concentration test is a more sensitive indication of renal impairment than the phenol-sulfonphthalein excretion.³⁷ Probably the most satisfactory modification of the concentration test is that of *Lashmet and Newburgh*:³⁸ After 10 P.M. on the day preceding the test

all food and fluid with the exception of a special diet (equivalent to 1900 calories, with 240 gm. of carbohydrate, 40 gm. of protein, 104 gm. of fat and 1 gm. of sodium chloride) are withheld from the subject. Urine samples are collected during the twenty-four hours of the test, and the specific gravity of each sample determined. Normal kidneys are able to concentrate the urine to a specific gravity of at least 1.029 while diseased kidneys are unable to raise the specific gravity to this level. The more severe the renal damage, the lower the urinary specific gravity.

A recent modification of the concentration test employs the antidiuretic effect of pituitary extract, and has the advantage that it requires little preparation of the patient and can be completed within a few hours.³² Five-tenths cc. of pituitary extract is injected subcutaneously and urine samples are collected every half-hour for three hours. Normal individuals will show a urinary specific gravity of 1.020 or greater, but patients with renal disease are unable to concentrate above 1.014. This test is perhaps preferable to the fluid restriction technic since it avoids prolonged restriction of fluids in patients who may be on the borderline of azotemia.

The results of the dilution tests are not as consistent as those of the concentration tests, although it is known that the kidneys of persons with far advanced renal disease excrete urine which is almost isotonic with blood plasma, and that the specific gravity remains "fixed" in the vicinity of 1.010. The *dilution test of Fishberg*⁴⁹ is satisfactory and in brief is performed as follows: The subject empties his bladder and drinks 1200 cc. of water within one-half hour, remaining in bed during the period of the test. Urine samples are collected every half hour for three hours, and the volume and specific gravity of each specimen is recorded. Normal individuals excrete nearly the entire 1200 cc. of ingested water within three hours, and the urine specific gravity approximates the low value of 1.002. Severe renal disease is associated with a failure to excrete more than a fraction of the recently ingested water, the total volume excreted during the three hours frequently being only 200 cc. The specific gravity remains in the neighborhood of 1.010.

Phenolsulfonphthalein Excretion

Phenolsulfonphthalein is excreted primarily by the renal tubular epithelium, 96 per cent of the dye which appears in the urine being eliminated by this route. Functional disturbance of the tubular epithelium is accurately reflected by diminution in the amount of dye excreted, although considerable glomerular damage may be present without decreasing dye excretion. Indeed, the renal hyperemia associated with acute glomerulonephritis may actually result in an increased rapidity in phenolsulfonphthalein elimination. The test has its greatest value in estimating the degree of renal impairment in cases of latent nephritis in which other routine examinations may still be relatively normal. Repeated performance of the procedure over considerable periods of time affords a method for determining the rapidity of progression of the disease process.

The most satisfactory technic for the test is that outlined by Chapman and Halstead^{41, 42} which is commonly known as the *fractional phenolsulfonphthalein test*: The subject empties his bladder and drinks 600 cc. of water (to insure an adequate flow of urine, which is essential for proper evaluation of dye excretion). After thirty minutes, 6 mg. of the dye are injected intravenously, urine collections are made in separate containers at fifteen, thirty, forty-five, sixty and 120 minutes after the injection, and the percentage of dye excreted in each specimen is estimated by comparison with standards.

Normal subjects promptly excrete the dye, the fifteen-minute specimen usually containing 30 to 50 per cent of the dye injected, and an additional 15 to 25 per cent appearing in the thirty-minute sample. Subsequent specimens contain steadily decreasing amounts of dye. The total excretion in normal individuals usually exceeds 70 per cent, and frequently is 85 to 95 per cent complete within two hours. Patients with nephritis show a much slower and less complete excretion, the fifteen- and thirty-minute samples often containing only 5 to 10 per cent of the total dye injected. There is also apparent fixation in the rate of excretion in nephritics, similar percentages being excreted in all the samples during the entire course of the two-hour test. A total excretion of less than 40

per cent indicates probable renal disease, while levels of 20 to 30 per cent usually connote definite severe nephritis. Excretion of less than 10 per cent in two hours suggests a fairly immediate fatal prognosis.

It must be emphasized that cardiac decompensation with chronic passive congestion, marked dehydration, and other conditions interfering with normal renal blood flow may produce a very marked but transient decrease in the excretion of phenolsulfonphthalein. The procedure should be deferred in patients suffering from such conditions, and even then it is always wise to repeat the test several times before drawing definite clinical conclusions from the results obtained.

TESTS OF HEPATIC FUNCTION

The multiplicity of hepatic functions has led to the development of numerous complex chemical tests, each designed to test a specific hepatic function. None of these procedures are diagnostic of any particular type of liver disease, however, and although they frequently indicate the severity of liver damage, practically they are not superior in this respect to several simpler and more easily performed clinical procedures. One of the commonest problems encountered in the study of patients with jaundice is whether the hepatic disease is due to obstruction of the common duct or to intrinsic hepatocellular disease.

The most valuable laboratory procedures in differentiating between these two conditions are the simultaneous and repeated (1) examination of the stool for the presence of bile, (2) estimation of the urobilinogen excretion and (3) determination of the icterus index.

Bilirubin in the Stool

The color of the stool is an adequate index of its bilirubin content, and as the amount of bilirubin decreases the color becomes first tan, then yellow, and finally with complete absence of bile, clay colored. Common duct stone seldom produces *persistent* complete biliary obstruction, and repeated stool examinations in such cases will show fluctuations in bilirubin content which are reflected by changes in color. Urin-

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Although the simple qualitative estimation of urobilinogen in serial dilutions of single urine specimens may prove valuable, it is by no means so informative as *quantitative* determinations carried out on twenty-four-hour urine collections. The *method of Watson*⁴³ is technically quite simple and depends upon the reduction of all urobilin to urobilinogen with ferrous hydroxide, and the reaction between urobilinogen, sodium acetate, and a modified Ehrlich's reagent (0.7 gm. of paradimethylaminobenzaldehyde, 150 cc. of concentrated hydrochloric acid, and 100 cc. of distilled water). A red color develops, the intensity varying directly with the amount of urobilinogen present. By comparing the color with phenol-sulfonphthalein standards and applying the formula developed by Watson, the urobilinogen excretion per day can be calculated. Aliquots of four-day collections of stool can be examined by a similar technic and the total excretion of urobilinogen readily determined.

TABLE 2
UROBILINOGEN EXCRETION IN JAUNDICE*

	Urobilinogen, Milligrams Per Day	
	Urine	Feces
1. Obstructive Jaundice		
Uncomplicated stone.....	0-6	10-250
Stone with cholangitis or biliary cirrhosis.....	4-50	10-250
Neoplasm.....	0-0.5	0-5
2. Hepatocellular Jaundice		
Cirrhosis.....	4-100	8-200
Hepatic disease with increased blood destruction....	20-200	300-1200
Acute hepatitis.....	4-200	10-300
3. Hemolytic Jaundice		
Uncomplicated.....	1-10	300-1800
Complicated by infection, anemia, hemolytic crises, infarction or anesthesia.....	10-300	300-2500

* After Watson, Arch. Int. Med., 59: 522, 1937.

Table 2 summarizes the usual range of urobilinogen excretion in common forms of liver disease as reported by Watson.^{43, 44} In general, low levels of urobilinogen in both urine and stool indicate biliary obstruction; high urinary urobilino-

ary urobilinogen excretion also fluctuates with the intermittent excretion of bile into the intestine, and gives useful confirmatory evidence of the nature of the obstruction. Biliary obstruction due to neoplastic disease, once it has developed, is complete and persistent, and the stools remain completely acholic and show no fluctuations in color.

Hepatocellular liver disease frequently produces a marked decrease in the amount of bile excreted into the intestine, and the stools may be clay colored for periods of many days. Completely acholic stools in toxic hepatitis are seldom persistent, however, and, as a rule, transient fluctuations in bile content similar to those noted in obstruction due to common duct stone are found. In contrast to the finding with stone, however, the urobilinogen excretion in the urine is much greater in hepatocellular disease because of the impaired excretory function of the hepatic parenchyma.

Urobilinogen Excretion

Urobilinogen is formed in the intestine by bacterial decomposition of bilirubin. Some of this urobilinogen is absorbed through the intestinal wall and appears in the blood. Most of this blood urobilinogen is removed by the liver and excreted in the bile, but small quantities leak through the kidney and normally 0.5 to 2.0 mg. appear in the urine in a twenty-four-hour period. If bile does not reach the intestine no urobilinogen is formed, and none appears in the urine. Very low levels of urinary urobilinogen almost always indicate biliary obstruction, and fluctuating levels suggest intermittent obstruction.

The ability of the liver cells to excrete urobilinogen is limited, and, as a consequence, slight parenchymal damage results in accumulation of excess amounts in the blood (provided bile is reaching the intestine), and larger amounts are excreted in the urine. Very high levels in the urine almost always indicate severe intrahepatic disease. Since biliary obstruction practically always results in some degree of hepatocellular damage, urinary urobilinogen in patients with this condition usually is increased, but seldom reaches the high levels observed in cases of toxic hepatitis.

Although the simple qualitative estimation of urobilinogen in serial dilutions of single urine specimens may prove valuable, it is by no means so informative as *quantitative* determinations carried out on twenty-four-hour urine collections. The *method of Watson*⁴³ is technically quite simple and depends upon the reduction of all urobilin to urobilinogen with ferrous hydroxide, and the reaction between urobilinogen, sodium acetate, and a modified Ehrlich's reagent (0.7 gm. of paradimethylaminobenzaldehyde, 150 cc. of concentrated hydrochloric acid, and 100 cc. of distilled water). A red color develops, the intensity varying directly with the amount of urobilinogen present. By comparing the color with phenol-sulfonphthalein standards and applying the formula developed by Watson, the urobilinogen excretion per day can be calculated. Aliquots of four-day collections of stool can be examined by a similar technic and the total excretion of urobilinogen readily determined.

TABLE 2
UROBILINOGEN EXCRETION IN JAUNDICE*

	Urobilinogen, Milligrams Per Day	
	Urine	Feces
1. Obstructive Jaundice		
Uncomplicated stone	0-6	10-250
Stone with cholangitis or biliary cirrhosis	4-50	10-250
Neoplasm	0-0.3	0-5
2. Hepatocellular Jaundice		
Cirrhosis	4-100	8-200
Hepatic disease with increased blood destruction	20-200	300-1200
Acute hepatitis	4-200	10-500
3. Hemolytic Jaundice		
Uncomplicated	1-10	300-1800
Complicated by infection, anemia, hemolytic crises, infarction or anesthesia	10-300	300-2500

* After Watson. Arch. Int. Med., 59: 522, 1957.

Table 2 summarizes the usual range of urobilinogen excretion in common forms of liver disease as reported by Watson.^{43, 111} In general, low levels of urobilinogen in both urine and stool indicate biliary obstruction; high urinary urobilino-

gen with normal or low fecal urobilinogen suggests intra-hepatic disease; and high levels in both urine and feces probably indicates hemolytic blood disease combined with hepatic impairment.

Bilirubinemia

Bilirubin accumulates in the blood as a result of excessive hemoglobin breakdown (*e.g.*, in hemolytic anemia), or because of hepatic or biliary tract disease with inability to excrete the bilirubin normally formed by the reticulo-endothelial system. Quantitative estimation of the amount of bilirubin present in blood plasma, and subsequent changes in this concentration during the course of liver disease are of considerable prognostic value since an increasing concentration indicates increasing severity of disease, while decreasing concentration indicates improvement. The degree of bilirubinemia is usually expressed in terms of the icterus index, or in actual milligrams of bilirubin per 100 cc. of blood as determined by the quantitative van den Bergh method. In the *icterus index method*, the color of the blood serum is compared with a standard solution of potassium dichromate (1:10,000), and the relative intensity is expressed in units, the normal values being between 4 and 6 units. Indices above 9 indicate latent jaundice, although clinical icterus may not be noted until the icterus index has reached 15. Blood pigments other than bilirubin (*e.g.*, carotene) occasionally may cause confusion, which may be avoided by use of the *quantitative van den Bergh reaction*. This procedure is based on the formation of azobilirubin, a reddish-violet compound, when bilirubin reacts with sulfanilic acid, hydrochloric acid and sodium nitrite.⁴⁴ The reaction is specific for bilirubin which can thus be detected in dilutions as high as 1 in 1,500,000. Normal blood serum contains up to 1.7 mg. of bilirubin per 100 cc.

The *qualitative van den Bergh reaction* is of value in differentiating the icterus associated with excessive hemolysis from that produced by liver disease, but since the urine is free from bile in the first instance, and contains bile in the second, the test actually has little practical diagnostic value.

Hippuric Acid Synthesis Test

It is probable that this test gives more information regarding the functional condition of the liver parenchyma than any other single test. It can be employed in both jaundiced and nonjaundiced patients, and when repeated serially is the best available index of the course of hepatic disease. The test depends upon the ability of the liver to convert benzoic acid to hippuric acid, which is subsequently excreted in the urine.⁴⁵ The subject in fasting state ingests 6 gm. of sodium benzoate, and urine is collected at hourly intervals thereafter for four hours. The hippuric acid is precipitated from each sample and weighed after drying.

Normal individuals excrete an amount of hippuric acid equivalent to 3 gm. of benzoic acid during the four-hour period. In patients with hepatic disease, the amount excreted is significantly reduced, the amount of reduction accurately indicating the severity of parenchymal dysfunction. In the presence of gastric retention or other conditions interfering with absorption from the gastro-intestinal canal, the sodium benzoate may be administered intravenously.⁴⁶ The test cannot be performed in patients with renal disease or dehydration of degree sufficient to interfere with the excretion of hippuric acid by the kidney, and it is wise to perform the urea clearance test simultaneously to rule out the presence of renal impairment.

White and his collaborators⁴⁷ have evaluated the hippuric acid excretion test and found it very helpful in prognosis, since it invariably gave low values in all severe and fatal cases of liver disease. It frequently indicated residual liver damage after subsidence of jaundice, and was also of value in ruling out liver disease in questionable cases. They found it of considerable assistance in assessing the surgical risk of patients with common duct stone and gallbladder disease. The postoperative course was favorable in those cases in which the hippuric acid excretion was between 2.5 and 3.6 gm. before operation, but when the excretion was between 1.0 and 1.5 gm. the postoperative course was prolonged and unsatisfactory. This test was of little value in differential diagnosis, since it showed some degree of reduction in practically every type of liver disease.

gen with normal or low fecal urobilinogen suggests intra-hepatic disease; and high levels in both urine and feces probably indicates hemolytic blood disease combined with hepatic impairment.

Bilirubinemia

Bilirubin accumulates in the blood as a result of excessive hemoglobin breakdown (e.g., in hemolytic anemia), or because of hepatic or biliary tract disease with inability to excrete the bilirubin normally formed by the reticulo-endothelial system. Quantitative estimation of the amount of bilirubin present in blood plasma, and subsequent changes in this concentration during the course of liver disease are of considerable prognostic value since an increasing concentration indicates increasing severity of disease, while decreasing concentration indicates improvement. The degree of bilirubinemia is usually expressed in terms of the icterus index, or in actual milligrams of bilirubin per 100 cc. of blood as determined by the quantitative van den Bergh method. In the *icterus index method*, the color of the blood serum is compared with a standard solution of potassium dichromate (1:10,000), and the relative intensity is expressed in units, the normal values being between 4 and 6 units. Indices above 9 indicate latent jaundice, although clinical icterus may not be noted until the icterus index has reached 15. Blood pigments other than bilirubin (e.g., carotene) occasionally may cause confusion, which may be avoided by use of the *quantitative van den Bergh reaction*. This procedure is based on the formation of azobilirubin, a reddish-violet compound, when bilirubin reacts with sulfanilic acid, hydrochloric acid and sodium nitrite.⁴⁴ The reaction is specific for bilirubin which can thus be detected in dilutions as high as 1 in 1,500,000. Normal blood serum contains up to 1.7 mg. of bilirubin per 100 cc.

The *qualitative van den Bergh reaction* is of value in differentiating the icterus associated with excessive hemolysis from that produced by liver disease, but since the urine is free from bile in the first instance, and contains bile in the second, the test actually has little practical diagnostic value.

BLOOD CHEMICAL VALUES IN HEALTH AND DISEASE—(Continued)

	Normal Range*	Commonly Increased in	Commonly Decreased in
Nonprotein nitrogen (blood) Total	25-35	Renal failure Dehydration Gastro-intestinal hemorrhage Acute yellow atrophy As above Gout Renal failure Late renal failure Acute yellow atrophy	Starvation Severe liver damage Nephrosis Acute infections
Urea nitrogen Uric acid Creatinine Amino acid	12-18 1.5-4.0 1-2 3-5		
Oxygen capacity (blood) Arterial	20 vol. per cent	Polythemia: primary or secondary	Anemia Carbon monoxide poisoning Methemoglobinemia
Venous	20 vol. per cent		
Oxygen saturation (blood)	95-100 per cent	High oxygen atmosphere	Mitral stenosis Congenital heart disease Pulmonary emphysema Pulmonary infection Asthma Emphysema
pH	7.35-7.45 units	Uncompensated alkalosis	Uncompensated acidosis
Phosphorus, inorganic (serum)	3.0-4.5	Terminal nephritis After major fractures Hyperparathyroidism Ingestion of excessive amounts of vitamin D	Hyperparathyroidism Osteomalacia Rickets
Phosphatase (serum)	1.5-4.0 units per 100 cc. (Bodansky) 0.2-0.5 units per 100 cc. (Kay)	Rickets Paget's disease Hyperparathyroidism Biliary obstruction Carcinoma metastatic to bone Myositis ossificans	
Proteins (serum) Total	6-8 gm. per 100 cc.	Multiple myeloma Kala-azar Scurvy Lymphoplastic venous thrombosis Dehydration	Malnutrition Nephrosis Cirrhosis
Albumin	3.6-5.4 gm. per 100 cc.		Renal disease Starvation Same as total protein
Globulin	1.5-5.4 gm. per 100 cc.	Same as total protein	
Albumin:globulin ratio	1.2-2.6		Nephrosis Cirrhosis Multiple myeloma
Sodium (serum)	315-330 135-145 mEq. l.	Dehydration	Addison's disease Profuse vomiting (gastro-intestinal obstruction) Terminal nephritis Diarrhea Diabetes
Salts, inorganic (serum)	1-5 0.5-1.0 mEq. l.	Renal failure	

* All values in mg. per 100 cc. unless otherwise specified.

* mEq. = milliequivalents per liter.

BLOOD CHEMICAL VALUES IN HEALTH AND DISEASE

	Normal Range*	Commonly Increased in	Commonly Decreased in
Amino acids (serum)	5-8	Acute yellow atrophy	Nephrosis Acute infections
Bilirubin (serum)	0.2-1.7	Biliary obstruction Toxic hepatitis Hemolytic anemia Pernicious anemia	Iron deficiency anemia
Calcium (serum)	9-11 4.5-5.7 mEq †	Hyperparathyroidism Extreme renal failure Overdosage with viosterol Hyperproteinemia	Hypoparathyroidism Renal rickets Infantile rickets Sprue, tetany Osteomalacia Hypoproteinemia
Carbon dioxide combining power (plasma)	40-50 vol per cent (children) 50-65 vol per cent (adults)	Alkalosis, pyloric obstruction, Ingestion of bicarbonate Hyperventilation	Acidosis, diabetic, renal Dehydration, starvation Emphysema
Chlorides (plasma)	362-376 576-620 (mg. NaCl per 100 cc.) 100-110 mEq †	Dehydration Acute and nephrotic glomerulonephritis Diarrhea of infancy	Excessive vomiting Terminal nephritis Diabetic acidosis Mercury bichloride poisoning Addison's disease Pneumonia, tuberculosis
Cholesterol, total (plasma)	150-250	Hypothyroidism Diabetes Fevers Biliary obstruction Pregnancy	Hyperthyroidism Malnutrition Acute hepatitis
Cholesterol esters (plasma)	110-145 60-70 per cent of total	Chronic glomerulonephritis Nephrosis Biliary obstruction	Acute hepatitis Chronic arthritis
Creatinine (blood)	1-2	Late renal failure	
Fibrinogen (plasma)	300-600	Acute and chronic infections Tissue necrosis	Acute yellow atrophy Chloroform and phosphorus poisoning
Glucose, fasting (blood)	70-90	Diabetes mellitus Cushing's syndrome	Hyperinsulinism Addison's disease
Hemoglobin (blood)	14-17 gm per 100 cc. (men) 13-16 gm per 100 cc. (women)	Polycythemia primary and secondary	Anemia
Iodine (blood)	3-20 micrograms per 100 cc.	Hyperthyroidism Iodine ingestion	Hypothyroidism
Icterus index (serum)	4-6 units	Hemolytic anemia Pernicious anemia Biliary obstruction Hepatitis, cirrhosis	Anemia of iron deficiency
Lipids, total (plasma)	500-550	Biliary obstruction Diabetes Nephrosis Xanthomatosis Hypothyroidism	Malnutrition Sprue Hyperthyroidism

* All values in mg. per 100 cc. unless otherwise specified.

† mEq = milli-equivalents per liter

BLOOD CHEMICAL VALUES IN HEALTH AND DISEASE—(Continued)

	Normal Range*	Commonly Increased in	Commonly Decreased in
Non-protein nitrogen (blood)		Renal failure	
Total	25-35	Dehydration Gastro-intestinal hemorrhage Acute yellow atrophy As above Gout Renal failure Late renal failure Acute yellow atrophy	Starvation
Urea nitrogen	12-18		Severe liver damage
Uric acid	1.5-4.0		
Creatinine	1-2		Nephrosis
Amino acid	5-8		Acute infections
Oxygen capacity (blood)			
Arterial	20 vol. per cent	Polycythemia: primary or secondary	Anemia Carbon monoxide poisoning Methemoglobinemia
Venous	20 vol. per cent		
Oxygen saturation (blood)	95-100 per cent	High oxygen atmosphere	Mitral stenosis Congenital heart disease Pulmonary congestion Pulmonary infections Asthma Emphysema
pH	7.35-7.45 units	Uncompensated alkalosis	Uncompensated acidosis
Phosphorus, inorganic (serum)	3.0-4.5	Terminal nephritis After major fractures Hypoparathyroidism Ingestion of excessive amounts of vitamin D	Hyperparathyroidism Osteomalacia Rickets
Phosphatase (serum)	1.5-4.0 units per 100 cc. (Bodansky) 0.2-0.3 units per 100 cc. (Kav)	Rickets Paret's disease Hyperparathyroidism Biliary obstruction Carcinoma metastatic to bone Myositis ossificans	
Proteins (serum)			
Total	6-8 gm per 100 cc	Multiple myeloma Kala-azar sarco d Lymphopothia ventrem Dehydration	Malnutrition Nephrosis Cachexia
Albumin	3.6-5.4 gm per 100 cc.		Renal disease Starvation Same as total protein
Globulin	1.5-3.4 gm per 100 cc.	Same as total protein	
Albumin-globulin ratio	1.2-2.6		Nephrosis Cachexia Multiple myeloma
Sodium (serum)	315-330 130-140 mEq †	Dehydration	Addison's disease Profuse vomiting (gastro-intestinal obstruction) Terminal nephritis Diarrhea Diabetes
Sulfates, inorganic (serum)	3-5 0.5-1.0 mEq *	Renal failure	

* All values in mg per 100 cc. unless otherwise specified
† mEq = milliequivalents per liter

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TREATMENT OF COMMON FORMS OF HEART DISEASE

HOWARD B. SPRAGUE, M.D., F.A.C.P.*

CARDIAC ASTHMA

CARDIAC asthma is a clinical syndrome of a paroxysmal, usually nocturnal, attack of orthopnea with wheezing respiration due, in most instances, to temporary failure of the left ventricle. If not relieved, it progresses to acute pulmonary edema. It most commonly occurs in patients with heart disease due to hypertension, coronary artery degeneration, or syphilis. It occasionally appears in patients with rheumatic heart disease with mitral stenosis, or marked aortic regurgitation, and in patients with calcific aortic stenosis. In addition to the acute pulmonary hypertension, during the attack there appears to be an element of bronchial spasm.

Diagnosis

The diagnosis is usually obvious; the difficulty, if any, is in the differentiation between cardiac asthma and bronchial or allergic asthma. Foreign body in the bronchus should, of course, be excluded. Most important is a history of heart disease of the types mentioned. In rare cases the attack is coincident with acute, painless coronary closure. In bronchial asthma, the patient is younger, or gives a story of years of asthmatic attacks or of an allergic background. Care should be taken, if the patient is not seen during the actual attack, to distinguish it from the periodic apnea of Cheyne-Stokes breathing which will arouse patients with a sense of air hunger.

SYMPTOMS AND SIGNS DURING AN ATTACK.—The patient is usually awakened by a sense of constriction in the chest and immediately feels it necessary to sit up to breathe. With this, there may be, as an early sign, prolonged expiration with

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ceed in trapping enough blood in the limbs effectively to reduce the venous return to the right heart and spare the overloaded pulmonary circuit. The pressure should be raised in the cuffs to just above the diastolic pressure in the limb. The constriction may be kept up for several minutes and one cuff at a time cautiously released to allow blood to return to the general circulation.

3. OXYGEN THERAPY.—To promote oxygenation of blood in the available alveoli in the lungs an atmosphere rich in oxygen should be supplied. This can be done by means of oropharyngeal insufflation, face mask, or oxygen tent. For oropharyngeal insufflation, a soft rubber catheter should be perforated near its tip through both walls in several axes by means of a red-hot safety pin. It is then lubricated with albolene and introduced into one nostril. The oxygen tube is connected and the oxygen is started at 6 to 8 liters per minute through a reducing valve and suitable water humidifier. The tube should be introduced until the tip rests in the oropharynx just above the point where the patient swallows oxygen on deglutition. The tip of the catheter will usually lie just behind the soft palate at the level of the uvula.

The face mask may be the transparent Barach type, or the Boothby, or some modification with a rebreathing bag.

In using the tent, attempt should be made to keep the concentration of oxygen as high as possible with the use of a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. If much pulmonary edema is present, the tent is the best method of administering oxygen.

4. DIGITALIS AND SIMILAR DRUGS.—For the relief of the individual attack of cardiac asthma, digitalis is generally too slow in its action. Some of the purified fractions, however, may be effective when given intravenously. If one is sure that the patient has not received any drugs of the digitalis series for at least two weeks prior to the attack, ouabain 0.25 mg. may be given intravenously and repeated once or twice at two-hour intervals and, if necessary, digitalization completed by mouth after recovery from the acute episode. *Lanatoside* —C is also useful for intravenous or intramuscular injection. The full digitalizing dose intravenously is 1.5 to 2 mg.

wheezing, or this may be preceded by a hacking, irritative, persistent cough. The violence of the episode may be so great that he goes to the window gasping for breath. There is often gray pallor, peripheral vasoconstriction, sweating, cyanosis, and distended neck veins. The liver may become engorged and tender. Rales of all types may be heard all over the chest, but they are mainly dry and squeaking at first, to be followed by coarse, moist bubbling rales if pulmonary edema supervenes. There is often so much respiratory difficulty and noise in the chest that the heart sounds are inaudible on auscultation. White, foamy sputum is coughed up, but, with increasing pulmonary edema, pinkish or bloody thin fluid may literally pour from the patient's mouth.

The pulse is rapid and thready. The rhythm may be normal or an ectopic rhythm, most frequently auricular fibrillation, may be present. The blood pressure in hypertensive patients is often elevated until the terminal stages of a severe or fatal attack.

Treatment

1. MORPHINE.—The first drug to be used in an attack of cardiac asthma is morphine. Whether or not this is combined with atropine makes little practical difference but there may be a slight advantage in the combination. Reduction of the patient's distress, suppression of the cough reflex, and depression of the respiratory center by morphine often succeed in terminating the attack. *Dosage:* $\frac{1}{4}$ grain, subcutaneously, repeated at fifteen-minute intervals for four doses, if necessary. For rapid effect this may be given intravenously. *Pantopon*, grain $\frac{1}{3}$ subcutaneously, may be used similarly, and also *dilaudid*, grain $\frac{1}{20}$.

2. MEASURES TO REDUCE VENOUS RETURN TO THE HEART.
—(a) *Venesection*.—Rapid removal of 200 to 500 cc. of blood from the antecubital vein with a large needle and syringe, or by actual incision of the vein, may be life-saving. The speed with which the blood is removed is, within limits, more important than the total quantity.

(b) *Constriction of Veins in Arms and Legs*.—By means of four blood pressure cuffs (Danzer technic) one may suc-

ceed in trapping enough blood in the limbs effectively to reduce the venous return to the right heart and spare the overloaded pulmonary circuit. The pressure should be raised in the cuffs to just above the diastolic pressure in the limb. The constriction may be kept up for several minutes and one cuff at a time cautiously released to allow blood to return to the general circulation.

3. OXYGEN THERAPY.—To promote oxygenation of blood in the available alveoli in the lungs an atmosphere rich in oxygen should be supplied. This can be done by means of oropharyngeal insufflation, face mask, or oxygen tent. For oropharyngeal insufflation, a soft rubber catheter should be perforated near its tip through both walls in several axes by means of a red-hot safety pin. It is then lubricated with albolene and introduced into one nostril. The oxygen tube is connected and the oxygen is started at 6 to 8 liters per minute through a reducing valve and suitable water humidifier. The tube should be introduced until the tip rests in the oropharynx just above the point where the patient swallows oxygen on deglutition. The tip of the catheter will usually lie just behind the soft palate at the level of the uvula.

The face mask may be the transparent Barach type, or the Boothby, or some modification with a rebreathing bag.

In using the tent, attempt should be made to keep the concentration of oxygen as high as possible with the use of a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. If much pulmonary edema is present, the tent is the best method of administering oxygen.

4. DIGITALIS AND SIMILAR DRUGS.—For the relief of the individual attack of cardiac asthma, digitalis is generally too slow in its action. Some of the purified fractions, however, may be effective when given intravenously. If one is sure that the patient has not received any drugs of the digitalis series for at least two weeks prior to the attack, ouabain 0.25 mg. may be given intravenously and repeated once or twice at two-hour intervals and, if necessary, digitalization completed by mouth after recovery from the acute episode. *Lanatoside* —C is also useful for intravenous or intramuscular injection. The full digitalizing dose intravenously is 1.5 to 2 mg.

(3 cat units). *Digitaline Nativelle*—1.25 mg. (3 cat units) in one dose by vein—produces full digitalization in six to ten hours or sometimes faster. Of the older preparations, *digifoline* and *digalen* are very effective intravenously. Three ampules may be given as an initial dose (3 cat units) and single ampules given at three-hour intervals if indicated.

5. *CORAMINE*.—Coramine—1 ampule administered intravenously—is a useful respiratory stimulant.

6. *CAFFEINE SODIUM BENZOATE*, OR *SALICYLATE*.—Seven and one-half grains of caffeine sodium benzoate, or salicylate, given intravenously also act as a useful respiratory stimulant.

7. *NITROGLYCERIN*.—Tablets of nitroglycerin, grain $\frac{1}{100}$, under the tongue, or *amyl nitrite* by inhalation are worth a trial.

8. *AMINOPHYLLINE*.—Aminophylline—0.48 gm. given slowly intravenously—will at times relieve an attack of cardiac asthma.

9. *EPINEPHRINE*.—In an occasional case of cardiac asthma with bronchial spasm, cautious trial of epinephrine—0.2 to 0.3 cc. given subcutaneously—may be attempted if anginal pain or coronary thrombosis are not factors in the attack.

Prevention of Attacks

Attacks of cardiac asthma may be averted by:

1. *Prevention of abdominal distention* by reducing the quantity of the evening meal.

2. *Reduction of fluid intake* to 1500 cc. daily.

3. *Sleeping with the head raised* on two or three pillows.

4. Regular use of *enteric coated ammonium chloride or nitrate* tablets, 3 to 6 gm. daily.

5. Administration of slowly acting *nitrites*—erythrol tetranitrate, or mannitol hexanitrate, $\frac{1}{4}$ to $\frac{1}{2}$ grain, three times a day.

6. *Aminophylline*—grains $1\frac{1}{2}$ to 3 taken by mouth four times a day. (Other xanthine drugs are also useful.)

7. Drinking *alcohol*, such as a small quantity of whisky or brandy at bedtime.

8. *Mercurials* (salyrgan, mercupurin) administered intramuscularly or intravenously—1 to 2 cc. once a week, or once

every two or three weeks continuously—will often prevent attacks.

ACUTE CORONARY OCCLUSION

Acute obstruction of a major coronary artery branch results in a fairly consistent train of events. This syndrome is usually referred to as "acute coronary thrombosis" and in most instances this will be the pathologic finding in cases coming to autopsy. To a definitely preponderating degree, the event is the expected result of atheromatous narrowing of the vessel with thrombosis in the region of sclerotic narrowing, atheromatous plaques, subintimal hemorrhage, or rupture of atheromatous abscess into the lumen. In younger individuals fibrotic narrowing of the artery may be the basis. In rarer instances, obstruction of the coronary ostia by syphilis or vegetations on the aortic valve, or embolism of the artery, is the cause of the occlusion.

Diagnosis

The chief factors in the history of patients stricken with acute coronary thrombosis are: (1) *previous angina pectoris* and (2) *hypertension*. Careful history taking will reveal previous chest distress on effort in most victims of such an attack. The knowledge of previous hypertension, which is found to be absent after the attack, is further supporting evidence.

SIGNS AND SYMPTOMS.—The signs and symptoms of a typical attack are too well recognized to give in detail. In general, they are: (1) severe substernal *pain* radiating to back, neck, arms and upper abdomen, and persisting for an hour to several hours and, in a less intense form, for a day or two or even longer; (2) *fall in blood pressure*, often a few hours after a primary rise during the acute pain; (3) evidence of *shock* as shown by pallor, sweating, cyanosis, vomiting, low pulse pressure and rise in pulse rate; (4) *fever* (usually not over 102° F.), and also leukocytosis, following onset of attack in twelve to twenty-four hours.

PHYSICAL EXAMINATION.—The *heart sounds* are usually decreased in intensity and there is often a gallop rhythm from left ventricular dilatation. *Abnormal rhythms*—heart block, premature beats, auricular fibrillation or ventricular tachy-

cardia—may be present. *Pericardial friction rub* is relatively infrequent, but when it does occur it is usually transient (one to three days) except in severe cases with fatal termination. A *systolic murmur* is commonly found at the apex and may appear in the first few hours. The *lungs* may show wheezy rales of mild cardiac asthma, or various grades of acute congestive failure, even to profound pulmonary edema, may ensue.

The electrocardiogram shows characteristic changes in S-T segments and T waves.

Treatment

Treatment may be divided into therapy of the acute attack and of the convalescent period.

ACUTE ATTACK.—Only two procedures are of much value during the acute episode: (1) the *relief of pain* by morphine, and (2) the *administration of oxygen*. Morphine should be given in sufficient quantity to reduce the pain to a tolerable level. It should be given in $\frac{1}{4}$ -grain doses, if necessary, every fifteen minutes for four doses. For rapid action, the first dose may be given intravenously. It should be remembered, however, that morphine need not be given routinely in such large amounts, and that sometimes $\frac{1}{2}$ grain of codeine sulfate administered subcutaneously may be just as useful and have less severe secondary gastro-intestinal effects. Pantopon, grain $\frac{1}{2}$, or dilaudid, grain $\frac{1}{20}$, may be substituted for morphine.

Oxygen should be administered, if possible, by one of the methods previously described.

GENERAL TREATMENT.—If evidence of the primary shock phase appears in a severe attack, it is usually wiser to move the patient to a comfortable bed at home, or preferably to a hospital if nearby, rather than to attempt to temporize in any makeshift situation where nursing will be difficult and inefficient. *Nursing care*, in fact, is of primary importance in all the stages of the attack.

Diet, while nausea or evidence of cardiac or vascular failure is evident, should consist of small amounts of water with sugar and gelatine, clear soup with salt (especially if the patient is sweating) and small amounts of whisky, brandy, or

cordials to provide sugar. Later, fruit juices, malted milk, jellies, gruel, and other soft solids may be added, always keeping each feeding small. A good combination of fruit juices is equal parts of orange and lemon juice sweetened with lactose. Black coffee is sometimes beneficial. The diet must be kept very light as long as any fever is present. At times, 6 to 8 drops of tincture of belladonna or charcoal tablets will counteract a tendency to distention and belching.

The *bowel* condition need not be considered in most cases for three to four days and then is best relieved by a small enema. Oil and agar preparations, or compound licorice powder, are good cathartics for patients suffering with acute coronary occlusion. If the attack is mild, or if the patient has much difficulty with a bed pan, I believe it is wiser to permit use of a commode chair by the bedside.

As early as can be tolerated, the patient should be encouraged to move the legs and feet about. These maneuvers, which should be allowed several times a day, while the patient is lying flat in bed, and also light leg massage, are useful in preventing stasis and thrombosis in leg veins and pulmonary embolism. *Drugs* are not regularly indicated. *Digitalization*, I believe, has no value in the acute failure of early coronary thrombosis unless the failure is complicated by auricular fibrillation or flutter, but is indicated if congestive failure appears after the shock stage is relieved. In such an event, digitalization by mouth may be completed in three to four days, giving about 1 grain, or 1 cat unit for every 10 pounds of body weight.

During the acute attack, there is some evidence to show that *intravenous aminophylline* (0.24 to 0.48 gm.) is beneficial. My own experience supports this to only a mild degree. I have not seen it do harm, however. In general, the use of xanthine drugs by mouth during convalescence is dependent upon the gastro-intestinal tolerance of the patient. They rarely give dramatic relief.

Quinidine, as a preventive of ventricular fibrillation, has been advocated, but I have not been convinced of the value of it. I have confined the use of quinidine to 6 to 9 grains a day for patients having many premature heart beats.

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matic pericarditis. It should not be attempted for relief of any such patient unless it can be shown that cardiac tamponade, and not cardiac dilatation and congestive failure, is the cause of the distress. Measures to combat failure should be tried first. Signs indicating cardiac tamponade are: (1) a pericardial friction rub, (2) rapid increase in cardiac size, (3) increase in the cardiac shadow across the base by x-ray, (4) distended neck veins, (5) orthopnea and epigastric pain, and (6) small pulse pressure and pulsus paradoxus.

Salicylates.—Aspirin or sodium salicylate should be tried in all cases of acute pericarditis. Aspirin can be given by mouth, 15 grains four times a day, or sodium salicylate in similar dosage with equal amounts of sodium bicarbonate or the salicylate alone in tap water by rectum.

Treatment of Congestive Heart Failure

The heart failure of acute rheumatic carditis in children is predominately that of the right side of the heart. The venous pressure is increased, the liver rapidly enlarges, the right side of the heart dilates as shown by x-ray, gallop rhythm appears, and the electrical axis of the electrocardiogram shifts to the right. Dyspnea or orthopnea do not appear early and the ability of the patient to lie flat without discomfort often permits edema of the face to ensue as part of a general mild anasarca.

Three drugs are of value in combating this type of heart failure. In decreasing order of value they are:

1. *Xanthine Drugs.*—Theocalcin (theobromine calcium salicylate) is one of the best tolerated. An average of 3 gm. a day by mouth can be administered over several weeks or months. Thesodate (theobromine sodium acetate) in similar doses we have found useful, and occasionally other members of this group.

2. *Mercurials.*—In cases resistant to xanthine drugs, or as a preliminary therapy, diuresis by intravenous mercurials is valuable. Salyrgan, salyrgan and theophylline, and mercupurin can be given beginning with a 0.5-cc. dose and then increasing to 1 cc. every three or four days, or less frequently as indicated. It is usually not necessary to administer am-

Sedatives, such as barbiturates (phenobarbital, grain $\frac{1}{4}$, three times a day) and bromides help to reduce the nervous tension and give rest. Small doses of morphine, codeine, or dilaudid may be necessary for several days after the acute episode.

Confinement to bed is variable. The progress of the patient may be judged by the temperature, pulse, blood pressure, electrocardiogram, white count, sedimentation rate, absence of gallop rhythm and cardiac failure, and freedom from pain. The shortest time in bed is three weeks, the average six, and the maximum may be several months.

ACUTE RHEUMATIC CARDITIS

The cause of rheumatic infection is unknown; and in the absence of typical acute polyarthritis or chorea, its diagnosis often depends upon the evidence of cardiac involvement during the course of an acute or subacute infection with equivocal joint symptoms.

Diagnosis

Minimal diagnostic evidence of rheumatic carditis is a prolongation of the P-R interval in the electrocardiogram beyond the duration normal for the given age period. Pericardial friction rub is another almost certain sign of rheumatic infection as is the development of an aortic diastolic murmur in childhood and adolescence. Systolic murmurs at the apex, and even mitral diastolic murmurs, can be considered as proof of heart involvement only if persistent after the acute infection has subsided. Definite cardiac enlargement occurring during an infection, associated with the development of murmurs, strongly suggests myocardial involvement.

There are only two important complications occurring during the course of active rheumatic carditis requiring specific therapy: (1) *acute pericarditis* and (2) *congestive heart failure*.

Treatment of Acute Rheumatic Pericarditis

Paracentesis.—It is practically never necessary, or even advisable, to perform pericardial paracentesis for acute rheu-

matic pericarditis. It should not be attempted for relief of any such patient unless it can be shown that cardiac tamponade, and not cardiac dilatation and congestive failure, is the cause of the distress. Measures to combat failure should be tried first. Signs indicating cardiac tamponade are: (1) a pericardial friction rub, (2) rapid increase in cardiac size, (3) increase in the cardiac shadow across the base by x-ray, (4) distended neck veins, (5) orthopnea and epigastric pain, and (6) small pulse pressure and pulsus paradoxus.

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monium chloride or nitrate in addition. The possible toxic effects of profound diuresis in a digitalized child should be avoided by omitting digitalis for at least three days prior to the use of the mercurial.

3. *Digitalis* is of much less value in the treatment of heart failure due to acute rheumatic carditis in children than in the congestive failure of adult life. It is likely to precipitate ectopic rhythms such as premature beats and auricular fibrillation. It should be discontinued if such arrhythmias occur during its use or if the P-R interval increases. Care should be taken to know the strength of the digitalis employed, but the total dose is comparable to that of the adult when correlated with the weight of the patient—1 cat unit or its equivalent for each 10 pounds of body weight. The present standardization in digitalis units (U.S.P. XI) should be recognized as supplying a stronger digitalis than formerly and only about two thirds of this dose can be given, unless the preparation used is standardized in cat units.

General Treatment.—There is no general treatment of rheumatic fever and its attendant carditis beyond bed rest, nursing, nutritional attention and symptomatic therapy. Confinement to bed is indicated until: (1) fever has been absent for two weeks, (2) white count and sedimentation rates are normal, (3) evidence of congestive failure has disappeared, (4) the P-R interval in the electrocardiogram is normal, (5) no subcutaneous nodules are present, (6) there is no chorea, and (7) the patient has had no respiratory infection or operation such as tonsillectomy within three weeks which might serve as a reactivating episode.

THE TREATMENT OF HYPERTENSION*

NORMAN H. BOYER, M.D.†

THIS discussion might, perhaps, have been entitled "Management of the Hypertensive Patient," for such a concept is more fruitful of good results than are efforts directed solely toward reduction of high blood pressure to normal. Those who concern themselves chiefly with blood pressure readings are doomed to frequent disappointment. While reduction of the blood pressure is desirable, and in some cases can be accomplished, it can be said at the outset that there is available today no specific single remedy for the reduction of high blood pressure. Despite this somewhat gloomy statement there is room for optimism in the management of hypertensive patients. Relief of symptoms and postponement of the dire results of increased pressure in the heart, brain and kidneys can often be accomplished. Realization and acceptance of this point of view should be reflected by the avoidance, on the part of both physician and patient, of undue emphasis on blood pressure readings.

ETIOLOGIC DIAGNOSIS

It is a medical truism that therapy is most effective when it is based upon a firmly established etiologic footing. Hypertension is a symptom which may depend upon one of many etiologic backgrounds. Thus a broad discussion of treatment must include a brief discussion of diagnosis, and for this purpose the accompanying tabulation, indicating some of the "causes" of hypertension, is inserted. The table and the following discussion are concerned only with diastolic hypertension. Elevation of systolic pressure with a normal or low

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in mind and particular attention must always be given to a careful urological survey.

Although the list of "causes" of hypertension is an impressive one, the great majority of patients with hypertension will have no demonstrable cause in nervous, endocrine, or renal symptoms. It is with the treatment of these patients with "essential" hypertension that we will be mainly concerned.

PATHOGENESIS

The pathogenesis of essential hypertension is not understood. The roles of heredity, psychological disturbances and renal ischemia have received attention and convincing evidence can be adduced that all are of some importance. There can be no doubt that hypertension is likely to be a *familial* disease. In this regard it should be emphasized that the offspring of such families are born with vulnerable vascular systems which differ from the normal only in their quantitative responses. They do not differ qualitatively from the normal and the responses to stimuli and vascular irritants, although exaggerated, are normal. Thus, in a susceptible individual any number of factors may act as precipitating or sustaining agents of vascular spasm. On the other hand, if the irritating factors should be sufficiently intense hypertension can be induced in a patient with a normally reactive vascular system.

It has been repeatedly observed that the *psychological pattern* of hypertensive patients is remarkably constant, although naturally not invariable. There commonly exists a strong undercurrent of fear and anxiety which appears to arise from strongly repressed aggressive tendencies. This aggressiveness often finds outlet in work and these patients frequently achieve more than average business success. The "self-made man" who, because of poverty, illness, or death, found himself thrown upon his own resources at an early age carries with him throughout his life the mark of inner fear bred of this early social insecurity.

Given a patient with hereditary vulnerability of his vascular system and the proper psychological, or other, aggravating factor, there ensues a period of years during which,

TABULATION

"CAUSES" OF DIASTOLIC HYPERTENSION

1. Neurological:

- (a) Psychic disturbances
- (b) Increased intracranial pressure
- (c) Midbrain and brain-stem lesions

2. Endocrine:

- (a) Pheochromocytoma of adrenal gland
- (b) Adrenal cortical adenoma
- (c) Pituitary adenoma (basophilism)
- (d) "Menopausal hypertension"
- (e) Ovarian tumors (?)
- (f) Toxemia of pregnancy

3. Peripheral arterial spasm or sclerosis:

- (a) Lead poisoning
- (b) "Essential hypertension"

4. Renal causes:

- (a) Acute or chronic glomerulonephritis
- (b) Chronic pyelonephritis
- (c) Polycystic disease
- (d) Renal tumors
- (e) Stenosis of main renal arteries
- (f) Renal arteriolar sclerosis
- (g) Coarctation of aorta
- (h) Amyloidosis
- (i) Infarction, trauma
- (j) Aberrant renal artery
- (k) Periarteritis nodosa, disseminated lupus erythematosus
- (l) Nephroptosis¹
- (m) Hydronephrosis
 - (1) Urethral stricture
 - (2) Prostatic obstruction
 - (3) Vesical neoplasms
 - (4) Pelvic tumors
 - (5) Calculus
 - (6) Ureteral stricture

diastolic pressure is a benign manifestation of (1) a very slow heart rate, (2) a sclerotic, inelastic aorta, or (3) increased cardiac output such as occurs in aortic regurgitation, hyperthyroidism and anemia.

It is beyond the scope of this presentation to dwell at length on the establishment of these various etiologic factors. Suffice it to say that these many possibilities must be kept

in mind and particular attention must always be given to a careful urological survey.

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Given a patient with hereditary vulnerability of his vascular system and the proper psychological, or other, aggravating factor, there ensues a period of years during which,

in most instances, there are no symptoms, but which is marked by intermittent, and later, by persistent hypertension. As the years advance organic changes begin to occur in the arterioles throughout the body and especially in the *kidneys*. These arteriolar changes are irreversible and eventually there may be enough renal arteriolar sclerosis to produce partial ischemia of the kidneys with the production of "renal" hypertension. At this stage the initial precipitating or aggravating factors are no longer necessary for the continuation of hypertension and their elimination will not necessarily affect the course of the hypertension.

THERAPEUTIC CLASSIFICATION

Proceeding on the basis of the foregoing hypothesis one can divide patients into four groups for the purposes of treatment and prognostication:

First, there are the patients with so-called "vasomotor instability." They may be symptomless or complain of nervousness, dizziness, headache, flushing, sweating, and coldness of the hands and feet. They show inordinate rises in blood pressure on slight provocation. They commonly have a blood pressure of 180 systolic and 95 to 100 or more diastolic in millimeters of mercury when first seen, but after a period of rest and reassurance, or on subsequent visits, the blood pressure is likely to be considerably lower or even normal. A fair proportion of such patients will go on to develop sustained hypertension, although some will become more stable in later years without any treatment. On the whole, this group is likely to respond well to therapeutic efforts.

The second group is comprised of patients with early or mild hypertension. The blood pressure is more uniformly sustained at a high level but occasionally is normal while the patient is at rest and falls to a considerable extent after the intravenous administration of pentothal sodium. There is either minimal sclerosis of the retinal arterioles or no eye-ground changes. The heart and kidneys are normal as ascertained by all available tests. This group also responds favorably to treatment.

A more advanced stage of the process will be found in the

third group whose blood pressure does not fall to normal with rest or sedation. The eyeground changes are more advanced, and there is evidence of cardiac or renal damage. Despite the advanced disease process some of these patients remain symptomless; or there may be headache, vertigo, visual disturbances, or symptoms referable to the heart or kidneys. At this stage it is apparent that therapeutic aims must become somewhat different from those entertained for the first two groups. When the arteriolar process has advanced to this degree the process becomes largely irreversible and treatment is directed mainly toward lessening the strain on vulnerable organs such as the heart, brain and kidneys.

Finally, there is the group with far advanced disease, marked eyeground changes, "fixed" hypertension, and cardiac or renal failure, or cerebral vascular disturbances. The treatment under such conditions becomes the treatment of the *complications* of hypertension and will receive little further attention here. Vigorous attempts to reduce the blood pressure in this group by present available measures is reprehensible.

TREATMENT

Symptomatic relief of a patient in the early stages of hypertension is relatively easy to attain and can be accomplished with the aid of a great variety of medicines, including placebos.² This is true because such symptoms depend more on neurosis than on the hypertension itself. This is indicated by the fact that many patients with an equal or greater degree of hypertension have no symptoms and by the fact that symptomatic relief is often achieved without any reduction of blood pressure. The patient improves because he feels he is now under the protective care of an individual of authority. For this reason, whatever treatment is used must be given with an air of confidence and enthusiasm but without rash prophecies which are likely to prove erroneous.

Rest

Mental and physical relaxation are our chief allies in the management of hypertensive patients. The kind and degree

in most instances, there are no symptoms, but which is marked by intermittent, and later, by persistent hypertension. As the years advance organic changes begin to occur in the arterioles throughout the body and especially in the *kidneys*. These arteriolar changes are irreversible and eventually there may be enough renal arteriolar sclerosis to produce partial ischemia of the kidneys with the production of "renal" hypertension. At this stage the initial precipitating or aggravating factors are no longer necessary for the continuation of hypertension and their elimination will not necessarily affect the course of the hypertension.

THERAPEUTIC CLASSIFICATION

Proceeding on the basis of the foregoing hypothesis one can divide patients into four groups for the purposes of treatment and prognostication:

First, there are the patients with so-called "vasomotor instability." They may be symptomless or complain of nervousness, dizziness, headache, flushing, sweating, and coldness of the hands and feet. They show inordinate rises in blood pressure on slight provocation. They commonly have a blood pressure of 180 systolic and 95 to 100 or more diastolic in millimeters of mercury when first seen, but after a period of rest and reassurance, or on subsequent visits, the blood pressure is likely to be considerably lower or even normal. A fair proportion of such patients will go on to develop sustained hypertension, although some will become more stable in later years without any treatment. On the whole, this group is likely to respond well to therapeutic efforts.

The second group is comprised of patients with early or mild hypertension. The blood pressure is more uniformly sustained at a high level but occasionally is normal while the patient is at rest and falls to a considerable extent after the intravenous administration of pentothal sodium. There is either minimal sclerosis of the retinal arterioles or no eye-ground changes. The heart and kidneys are normal as ascertained by all available tests. This group also responds favorably to treatment.

A more advanced stage of the process will be found in the

chological attitude and behavior, and this influence might as well be good as bad.

For the most part, one has only to be a sympathetic listener after inducing a patient to talk about himself as a person and not as a medical problem. One will thus often uncover sources of stress and strain. Thereafter, simple suggestions as to mode of living and philosophy of life will often suffice. Houston⁴ aptly phrased psychotherapeutic aims in hypertension as follows: "It may prove helpful to realize that the 'will to power' as celebrated in success magazines and popular success psychologies constitute propaganda for emotional habits and attitudes which may in some instances be baneful, and that the doctor himself may be a therapeutic agent of great value if he can successfully propagandize and institute a different habit, the habit of equanimity"

Diet

Fads and fancies in the dietary treatment of hypertension have come and gone with some regularity, but at present the consensus is that *moderation* should be the keynote. In the absence of nitrogen retention in the blood there is no need for drastic protein restriction. Indeed, if the dietary protein is reduced below the daily needs of 50 to 70 gm. for the average adult, the body proteins will be used and the result may be very undesirable depletion of the blood proteins. Drastic restriction of salt is not necessary unless there is edema. Many individuals do ingest large amounts of salt, however, and for these patients it may be desirable to limit the intake of salt to that used in the preparation and to discourage the use of salt at the table. Some patients seem to have less headache and dizziness when the salt intake is moderately restricted. Highly seasoned foods and spices are best avoided, as the volatile oils contained therein are said to be vascular irritants.⁵

The most important dietary consideration is the *control of obesity*. Many hypertensive patients are overweight, and reduction in blood pressure often parallels reduction in weight. Even if no reduction in blood pressure occurs, the correction of obesity will protect the heart against the increase in work

of rest will depend, in large measure, on the severity of the disease and the presence of complications. On the whole, it is wise to allow as much normal activity as seems justified by the state of the heart, renal and cerebral circulations. It is often as harmful to greatly restrict patients in the early stages of hypertension as it is to allow unrestricted activity in those with signs and symptoms of diminished cardiac reserve. As previously indicated, the business and social pursuits of these patients often act as vents for releasing pent-up aggressive tendencies. To prohibit these activities only serves to increase the inner tension.³ Physical activity may often induce mental relaxation and the cultivation of a hobby is to be strongly recommended.

A good night's rest of eight to nine hours is essential and the judicious use of the barbiturates may help in this regard. The patient should be induced to break up the day by resting for an hour or so after lunch and he should be persuaded to give up evening work.

Since it is known that physical exercise raises the blood pressure in normal individuals and to a much greater extent in hypertensive patients, hard physical work and play is to be avoided. On the other hand, mild forms of exercise such as walking, leisurely golf, and horseback riding are to be recommended for all but the far advanced cases with complications. Most patients afflicted with hypertension cannot play cards with equanimity, and this pastime should be discouraged. Even without stakes, winning is important to these individuals, and it should be remembered that the pleasurable emotion of winning will induce quite as much rise in blood pressure as the less pleasurable prospect of losing.

Psychotherapy

Physicians instinctively shy away from this term which conjures to their minds the mysteries of the subconscious and the abstraction of Freudian language. Formal psychoanalytic sessions are not required for the psychotherapeutics of most patients with hypertension, although, occasionally, the services of a trained psychiatrist will be needed. Physicians ought to realize that they cannot avoid influencing a patient's psy-

chological attitude and behavior, and this influence might as well be good as bad.

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The most important dietary consideration is the *control of obesity*. Many hypertensive patients are overweight, and reduction in blood pressure often parallels reduction in weight. Even if no reduction in blood pressure occurs, the correction of obesity will protect the heart against the increase in work

which moving 20 to 50 or more pounds of excess fat with each step entails. For the really obese it usually is not sufficient to give such vague instructions as, "Cut out sweets and starches." Detailed dietary instructions must be given. A 1000-calorie diet will usually produce gradual weight loss in individuals doing light sedentary work. More active individuals may require 1500 or, rarely, 2000 calories a day. For patients who lack the requisite will power to adhere to the diet the institution of rigid salt restriction may make the food so unpalatable as to assist greatly in the reducing campaign.

There is no need for either restricting or forcing large amounts of fluid unless there is, respectively, cardiac or renal failure. Fluid intake should be adequate to insure a daily urine output of 1000 to 1500 cc. Coffee and tea need not be interdicted, although they are best avoided at night when they may interfere with sleep.

Tobacco and Alcohol

Much has been said and written on the pros and cons of the use of tobacco and alcohol, not a little of which has seemingly been based on the author's personal taste or moral sense. In general, it may be said that the available evidence, especially in the field of peripheral vascular disease, points toward tobacco as a vascular irritant and therefore is best avoided. There is nothing to suggest that tobacco is a cause of either hypertension or vascular disease, but there is reason for believing that it may be very irritating to a vulnerable vascular tree. It is certain that some individuals are very susceptible to tobacco and in them the smoking of one cigarette can produce a rise of 40 or more millimeters of mercury in the systolic and 20 mm. or more in the diastolic pressure. For such individuals tobacco is a distinct poison and should be absolutely interdicted. On the other hand, it may be unwise to attempt abrupt modification of deeply ingrained habits, especially in the elderly. Gradual modification will keep these patients happier and more cooperative.

Alcohol has been accused of causing hypertension, just as all other evils, at some time or other, have been laid at its

door. There is no evidence whatever that alcohol is either an initiating or aggravating factor in arterial hypertension. On the contrary, if used intelligently, it can be of great service to hypertensive patients. Alcohol in moderate amounts is a good sedative and, for the elderly patient, is one of the best we possess. Furthermore, it has readily available food value and under certain circumstances may well be used for this purpose although it, naturally, is not to be preferred to other foodstuffs containing essential vitamins and minerals. Finally there are reasons for believing that alcohol may have a slight vasodilator effect and this certainly does the hypertensive patient no harm.

The main disadvantages in the use of alcohol revolve around the likelihood of inducing excesses in eating, smoking, and emotional and physical experiences. These excesses depend, of course, on consumption of a larger amount of alcohol than would ordinarily be considered therapeutic.

Sedatives

Drugs which have a quieting action on the higher nerve centers have come to be the mainstay in the medicinal attack on hypertension. Their purpose, when given in repeated small doses throughout the day, is to level off the emotional fluctuations of blood pressure and to induce a state of tranquility. For this purpose the *bromides* are well suited. One gram (15 grains) of the triple salts of bromide (sodium, potassium, and ammonium bromide) may be given from two to four times a day and can be continued for long periods if the patient is under observation and the possibility of bromidism is kept in mind. The *barbiturates*, especially phenobarbital, are also widely used for this purpose but tend to lose their efficacy after prolonged use. It is not necessary to induce a state of "grogginess" and ordinarily 0.016 to 0.032 gm. ($\frac{1}{4}$ to $\frac{1}{2}$ grain) of phenobarbital three or four times a day is sufficient.

Another indication for the use of sedatives is to insure an adequate period of sleep at night. Many patients will not need this help but if a patient is troubled by insomnia it is important to inquire whether sleeplessness occurs on first retiring

which moving 20 to 50 or more pounds of excess fat with each step entails. For the really obese it usually is not sufficient to give such vague instructions as, "Cut out sweets and starches." Detailed dietary instructions must be given. A 1000-calorie diet will usually produce gradual weight loss in individuals doing light sedentary work. More active individuals may require 1500 or, rarely, 2000 calories a day. For patients who lack the requisite will power to adhere to the diet the institution of rigid salt restriction may make the food so unpalatable as to assist greatly in the reducing campaign.

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very small for some patients and fatalities have been recorded in which the serum level was little above the safe range indicated above. Because the rate of renal excretion of the drug varies considerably, varying not only with renal function but also from case to case with normal renal function, the drug should never be given without careful control of the blood level.*

A safe procedure is to start with 0.3 gm. (5 grains) of the thiocyanate twice a day for one week. At the end of that time the blood level is determined and the dose increased or decreased, usually the former, according to the patient's symptoms, level of blood pressure, and amount of thiocyanate in the blood. The aim of treatment is, of course, to obtain an adequate hypotensive effect with the least possible thiocyanate and carefully to avoid more than 14 mg. per 100 cc. of thiocyanate in the blood. The maintenance dose may vary from 0.3 gm. (5 grains) a week to 1 gm. (15 grains) a day.⁶ After the dosage has been adjusted, blood thiocyanate determinations must be periodically checked every three or four weeks since there may be unexplained fluctuations in the blood level on constant dosage. The hypotensive effects are not always apparent immediately, so that treatment should be continued for several weeks before judgment as to its efficacy is undertaken.

Reactions.—The majority of patients undergoing cyanate therapy will have sensations of weakness and fatigue during the early weeks of treatment. In some this appears to be due to the hypotensive effect of the drug while in others it must be considered as a direct effect of the cyanate. This effect usually disappears from the second to the sixth week of therapy.⁶ There may be an associated aching and cramping in the calf muscles. Another common complaint, occurring even with "safe" blood levels of cyanate, is of mild gastrointestinal disturbances such as anorexia, abdominal discomfort, nausea, or vomiting. Itching skin eruptions also occur occasionally but usually promptly disappear after withdrawal

* A kit for performing office determinations of blood thiocyanate, which has an accuracy adequate for clinical purposes, is available from Eli Lilly Company.

or in the early morning hours. For the former the rapidly acting barbiturates, such as pentobarbital sodium (nembutal) in doses of 0.1 to 0.2 gm. ($1\frac{1}{2}$ to 3 grains), are indicated, whereas the longer acting barbiturates, such as phenobarbital in doses of 0.1 gm. ($1\frac{1}{2}$ grains) at bedtime, are preferable if sleep in the latter part of the night is disturbed.

Nitrites and Nitrates

The duration of action of the nitrites, such as amyl nitrite, nitroglycerin, sodium nitrite and erythrol tetranitrate, is altogether too brief to be of any value in controlling the hypertensive state, and their sudden, often profound, temporary effect is not entirely without danger. The nitrites are, of course, indicated in the treatment of acute crises, such as angina pectoris, in hypertensive patients.

The use of the more slowly acting nitrates in an effort to produce a gradual and prolonged hypotensive effect has more to recommend it. The nitrate ion is not absorbed but is slowly reduced to the nitrite form in the intestinal tract and is then presumably absorbed in small quantities over a long period of time. For this purpose bismuth subnitrate, in capsules of 0.7 gm. (10 grains), given three times a day, or mannitol hexanitrate, in doses of 0.016 to 0.032 gm. ($\frac{1}{4}$ to $\frac{1}{2}$ grain), two or three times a day, may be used. Individuals may lose their susceptibility to nitrites after a time, but this is quickly regained after a vacation from the drug for a few days to a week or so.

Thiocyanates

Sodium or potassium sulfocyanate has been used in the treatment of hypertension for many years by different investigators and with a varying degree of enthusiasm. The drug is very toxic and can produce death. According to Wald, Lindberg and Barker,⁶ however, toxic manifestations do not appear unless the blood level of thiocyanate rises to 15 mg. per 100 cc. and fatalities do not occur until a level of 40 to 50 mg. per 100 cc. is reached. They consider the optimum safe therapeutic range to be from 8 to 14 mg. per 100 cc. Nevertheless, the margin between therapeutic and toxic doses is

sive patient, it is worthwhile to remove as many of the aggravating factors as possible, including the often disturbing psychic and physical disturbances of the menopause.

There appears to be real hope on the horizon for the hypertensive patient in the form of *kidney extracts*.^{7, 8} As yet these substances have not been obtained in pure form and are not available commercially.

Surgical Treatment

Surgical removal of adrenal tumors when present is, of course, indicated. In addition, the surgical attack on the genito-urinary tract in hypertensive patients has received a great deal of recent attention.

Nephrectomy.—A goodly number of cures by nephrectomy and other surgical procedures has been reported, especially when unilateral kidney disease has been demonstrated. Unfortunately most of the reported successes have been in children or young adults which make up the smallest age group of the total patients with hypertension. Of 212 patients studied by Palmer et al.,⁹ 22 per cent had deformities of pelves or ureters as demonstrated by intravenous urography. In most instances these deformities were considered to be incidental. Nine patients were subjected to unilateral nephrectomy and of these only one showed improvement in the hypertension. The authors conclude that, in general, females over forty-five or males over fifty years of age should not be advised to have nephrectomy for hypertension even though unilateral lesions can be demonstrated.

In arriving at a decision to perform nephrectomy one should take into account not only the age of the patient, but the duration of the hypertension and of the renal lesion, if this can be established, the family history, and the degree of vascular damage as estimated from eyeground examination. If a patient has a strong family history of hypertension it is more than likely that whatever unilateral renal changes which may be demonstrated are entirely incidental. This undoubtedly explains why other patients with identical anatomical kidney changes do not develop hypertension. Furthermore, even if the unilateral lesion were the initiating

of the drug and do not necessarily contraindicate further trial of the drug at a later date.

More serious toxic manifestations appear when the blood cyanate level becomes high. These manifestations consist of more severe nausea and vomiting, diarrhea, exfoliative dermatitis, vascular collapse, and cerebral manifestations such as slurring of speech, aphasia, confusion, delirium and coma.

In addition to the direct toxicity of thiocyanate, undesirable reactions due to the hypotensive effect at times occur in arteriosclerotic subjects. The more important of these consist of cerebral thrombosis, and increase in attacks of preexisting angina pectoris or in its onset if previously absent.

It is evident that thiocyanate cannot be considered the ideal therapeutic agent. It should certainly not be used until other less dangerous methods have been tried and proved unsuccessful. It should never be used except in cooperative patients under close observation and with the blood cyanate level controlled. It should be used most cautiously, if at all, in the treatment of the elderly arteriosclerotic patient or in treatment of those with evidence of myocardial or renal complications.

Miscellaneous Drugs

Such preparations as garlic, parsley, mistletoe and watermelon seed have never been shown to be effective in lowering the blood pressure of hypertensive patients under rigidly controlled conditions. Whatever success has been attained in individual cases can probably be attributed to a form of psychotherapy which accompanies the enthusiastic administration of any drug, even dilute hydrochloric acid.² Similarly there is no experimental or clinical evidence to suggest that the xanthines have a depressor effect upon patients in the hypertensive state.

In women with hypertension or vasomotor instability during the menopause, the use of *estrogenic substances* may be of benefit. It is more than probable that the disturbance at the menopause only acts as an aggravating factor in a patient with an inherently vulnerable vascular system. In conformity with our expressed intention of "managing" the hyperten-

contraindications a patient with *early* malignant hypertension, or patients who have shown absolute or relative failure to respond to an adequate trial of more conservative management, may well be advised to have the operation performed.

Nephro-omentopexy.—The subject of the surgical attack on hypertension should not be left without brief mention of the attempts to increase renal blood flow by grafting omentum or muscle onto the kidney. Such attempts were a natural consequence of the demonstration of the importance of decreased renal blood flow in experimental hypertension. In patients in whom hypertension results from obstruction to the main renal arteries the operation is logical, but these are few and there is no practical way of demonstrating obstruction to the main vessels during life. On the other hand, it has not been demonstrated that the operation is without value even when the decreased renal blood flow is due to changes in the smaller intrarenal vessels for in such cases increasing the flow to the tubules alone may be of some benefit. Needless to say, this operation is at the present even more experimental than those upon the sympathetic nervous system.

Miscellaneous Measures

Foci of infection should be searched for and eliminated, not so much because such foci are likely to be direct causes of hypertension, but because anything which improves the general health of the patient is likely to be favorably reflected in the level of the blood pressure. The *bowels* should be regulated in an effort to avoid straining at stool and not primarily because "auto-intoxication" is a factor in the production of hypertension. Rupture of small cerebral vessels not uncommonly is produced by straining and may result in fatal hemorrhage.

SUMMARY AND CONCLUSIONS

It must have become evident during this discussion that, although there is no one specific measure which is universally effective in the treatment of hypertension, a great many things can be done for the hypertensive patient. The ther-

factor in the hypertension there is reason to believe that after the process has continued for several years the resulting arteriolar changes in the "normal" kidney may sustain the high blood pressure.¹⁰ When the duration of the hypertension and renal lesion cannot be established, the finding of well advanced arteriosclerotic retinopathy should warn against over-enthusiasm for urological procedures.

Partial adrenalectomy and denervation of the adrenals has been advocated and tried in the treatment of hypertensive patients, but without outstanding success.

Splanchnicectomy.—Resection of the splanchnic nerves has enjoyed more popularity, and rightly so. The status of splanchnicectomy has been somewhat confused by the gradual metamorphosis of opinion as to the operation of choice. It now appears that the early operations (such as removal of the second, third and fourth lumbar ganglia with the sympathetic trunk, section of the anterior nerve roots bilaterally from the sixth thoracic to the second lumbar segments, resection of the celiac ganglia, supradiaphragmatic splanchnic resection, and infradiaphragmatic splanchnic resection) are all procedures inferior, for one reason or another, to the transdiaphragmatic splanchnic resection described by Smithwick.¹¹ Unfortunately the patients showing the best results from all these surgical procedures are also the ones who often do well on medical management, namely, those with early or mild hypertension, and the percentage of reported successes is not significantly greater with surgical than with medical treatment. Whether the ultimate course will be more favorable in the operated cases can be decided only after years of observation. It is too early to evaluate completely the surgical treatment of hypertension and resection of the splanchnic nerves must still be considered as an experimental procedure.

There are definite contraindications to splanchnicectomy which, according to de Takats et al.,¹² are: (1) malignant hypertension with renal insufficiency (but not necessarily early malignant hypertension), (2) cardiac decompensation, (3) nitrogen retention, (4) severe atheromatosis of large vessels, and (5) age over fifty years. In the absence of these

contraindications a patient with *early* malignant hypertension, or patients who have shown absolute or relative failure to respond to an adequate trial of more conservative management, may well be advised to have the operation performed.

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SUMMARY AND CONCLUSIONS

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apeutic aims may be summarized as directed toward the control of symptoms, the postponement of complications, and the actual reduction of blood pressure. The general hygiene and body and mental habits should receive attention and a state of tranquility striven for with the help of informal psychotherapy and the judicious use of sedatives. These measures alone will often relieve symptoms and reduce the blood pressure. In addition, the use of the longer acting nitrates or of sulfocyanate may produce further symptomatic relief or manometric success. Finally, in those patients in whom these measures fail and in whom there is reason to believe that the disease will progress inexorably to death within a few years, surgical attack on the splanchnic nerves, with or without nephro-omentopexy, should be advised provided none of the contraindications discussed above are present.

High blood pressure is one of the leading causes of disability and death. There is every reason to hope that the brilliant progress now being made in the study of experimental hypertension will soon yield information of practical value in clinical hypertension. In the meantime, patients suffering from high blood pressure deserve all the time and effort which we have at our disposal to give them.

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COMMON PROBLEMS IN THE TREATMENT OF ANEMIA*

MAURICE B. STRAUSS, M.D.†

THE diagnosis and treatment of blood disorders in general practice was outlined in these clinics two years ago. Today there will be considered certain specific problems commonly arising in the diagnosis and management of patients with anemia. It is hardly necessary at this time to amplify the fact that *precise diagnosis* is the fundamental prerequisite of successful treatment of anemia. Whenever possible the *etiology of the anemia in the individual patient* should also be elicited. Finally, it is to be stressed that the treatment of anemia lies not merely in the exhibition of this or that drug but in the treatment of *the patient as a whole*. Case records have been selected not for unusual aspects or for the completeness of data but because they represent common problems and illustrate how these may be managed.

CASE I. PERNICIOUS ANEMIA SIMULATING GALLBLADDER DISEASE. MANAGEMENT IN THE HOME IN A PATIENT REFUSING HOSPITALIZATION

Five weeks prior to examination a sixty-three-year-old housewife was seized with acute right upper quadrant pain and vomiting, followed by increasing anorexia, "indigestion," belching of gas and constipation. Vomiting of unchanged food or bile-stained mucus was frequent. Weight and strength declined. After three weeks the patient took to her bed. On several occasions she was told that she was jaundiced. Pallor had not been noted. On a number of occasions smarting of the tongue had been present. For ten days constant numbness in the feet had been an annoy-

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ing symptom. During the fortnight immediately preceding examination the patient developed a conviction that she had either cancer or gallstones and that if she were to have an operation she would not survive. Accordingly she was adamant in refusing hospitalization for study and treatment. She was sure her condition was hopeless and that it was not worthwhile doing anything about it. This frame of mind was in distinct contrast to her previous cheerful energetic personality. Her past history was unimportant save for a lifelong story of poor digestion. She had never cared for or eaten much meat.

Examination showed a very tired-looking woman, with a sal-low complexion, lying comfortably in bed. The sclerae were subicteric and the mucous membranes showed moderate pallor. The tongue, although not atrophic, was definitely reddened and lacked a normal coat. The radial arteries were thickened; the pulse was of normal tension. A well-marked systolic murmur was best heard over the base of the heart. Tenderness without muscle spasm was present in the epigastrium, especially on the right. Position and vibration sense in the feet was definitely diminished. Rectal examination was negative. (The gloved finger was smeared on a glass microscopic slide for later examination.) Pelvic examinations showed an atrophic uterus. Otherwise, physical and neurological examinations showed no deviation from normal. The temperature, pulse, respiration and blood pressure were normal.

COMMENT.—Obviously the patient was seriously ill and could best have been studied and treated in a hospital. The picture presented pointed to gallbladder disease or gastro-intestinal cancer. Although the patient appeared moderately anemic, this might well have been the result of the primary disorder. However, both the glossitis and the recent *persist-ent* paresthesias of the feet suggested pernicious anemia. If this were the correct diagnosis one would have been justified and well-advised in deferring roentgenologic examination until this had been treated.

Since a positive diagnosis of pernicious anemia can be most easily established by observing a *reticulocyte response to specific therapy* the following procedure was employed: Five cubic centimeters of blood, withdrawn from the antecubital vein, were placed in a vial in which had been dried 0.2 cc.

of a mixture of 2 per cent potassium oxalate and 3 per cent ammonium oxalate. Next, the patient received by intragluteal injection 5 cc. (75 U.S.P. injectable units) of a concentrated liver extract. A specimen of urine was obtained.

The family was instructed to *continue allowing the patient to sit in a chair* but was cautioned not to allow her out of bed without assistance because of the danger of falling. It was felt that the dangers involved in allowing this woman to sit up, as she had been doing, were less than those associated with complete bed rest, such as hypostatic accumulation of fluid in the lungs. The patient was urged to continue taking warm fluids freely but not to force herself to take solid food in any quantity until she felt like so doing. No opiates were prescribed owing to their frequent ill effects in pernicious anemia in severe relapse.

Later, in the laboratory, films, both plain and stained for reticulocytes, were made from the oxalated blood. Should a long delay have been anticipated between the time of withdrawing blood and the arrival at the laboratory, these would have been made at the bedside from capillary blood obtained by puncture of the ear lobe. The results of the various examinations follow:

Red blood cells	1,610,000 per cu. mm.
White blood cells	4,200 per cu. mm.
Hemoglobin	48 per cent (7.5 gm. per 100 cc.)
Icteric index	15
Hematocrit	21.8 per cent
Mean corpuscular volume	135.4 cu. micra (normal 85 to 95 cu. micra)
Mean corpuscular hemoglobin concentration	34.4 per cent (normal 33 to 35 per cent)
Differential:	
Polymorphonuclear neutrophils	46 per cent
Small lymphocytes	43 per cent
Large lymphocytes	6 per cent
Monocytes	5 per cent

Tiny microcytes and large oval macrocytes were frequent. There was marked variation in the size and shape of the erythrocytes. Occasional polychromatophilic cells were seen.

The platelets were reduced in number. The polynuclear cells were quite mature, many having five and six lobes to the nucleus. The reticulocytes numbered 2.3 per cent.

The urine was amber with a specific gravity of 1.016. A slight trace of albumin was present. Sugar and bile were absent. Urobilinogen was present in dilution of 1:32 (control 1:8).

Following rectal examination a glass slide had been smeared with fecal material. This was flooded with benzidine solution. No blue color was observed, indicating that no occult blood was present.

Forty-eight hours later it was reported that the patient was feeling much better and that she had developed an interest in food. It was suggested that meat and eggs be given daily.

On the sixth day the patient was revisited. She was obviously brighter and looked less tired. She stated that her appetite was better than it had been for years and that she had had little indigestion. No redness of the tongue was present nor had any soreness been noted during the past four days. Blood films on cover slips containing a dried coating of brilliant cresyl blue were obtained. Two cubic centimeters (30 units) of liver extract were administered intramuscularly. The patient was urged to eat meat, eggs, fruit and vegetables daily. She was advised to continue her bed-and-chair existence. The reticulocytes were found to number 32.6 per cent.

Two weeks later the patient had gained 6 pounds, was entirely free of symptoms, and had been walking about the house unassisted. She was again given 30 units of liver extract intramuscularly and venous blood was withdrawn for examination. The red blood cells numbered 3,600,000 per cubic millimeter and the hemoglobin was 64 per cent (10 gm. per 100 cc.). The reticulocytes were 1.1 per cent. At this time, when the patient was quite thoroughly impressed with her dramatic improvement, the need for constant treatment was emphasized. It was pointed out that *relapse always occurs sooner or later if treatment is omitted*. It was further stressed that, although at the moment she might think she would never lapse in treatment, after a few years she would be likely to forget her now recent disabilities. In view of the fact that

the diagnosis of pernicious anemia had now been unequivocally established by the therapeutic response to liver extract alone, and, since there was now a lag in hemoglobin production, iron, as tablets of ferrous sulfate (4 grains each), to be taken after each meal, was prescribed.

A fortnight later, since the red cells numbered 4,110,000 per cubic millimeter and the hemoglobin content was 78 per cent (12.2 gm. per 100 cc.), the patient was now allowed gradually to resume her full activities. After six weeks of iron therapy, the hemoglobin having reached 87 per cent, ferrous sulfate was omitted. Although all abdominal pain and gastrointestinal symptoms had disappeared, cholecystograms were obtained at this time, since approximately 20 per cent of patients with pernicious anemia *also* have gallbladder disease. However, a perfectly normally functioning gallbladder was shown in the films.

Biweekly injections of 30 units of liver extract were continued for six months. The patient's red blood cells then numbered 4,510,000, the hemoglobin was 93 per cent. There had been no symptoms referable to the digestive tract or the nervous system and there was a gain of 28 pounds in weight. Injections were now reduced to 15 units biweekly. At the end of a year from the first observation, all symptoms remaining in abeyance and blood values remaining normal, the interval between injections was lengthened to three weeks.

CASE II. PERNICIOUS ANEMIA SIMULATING PERIPHERAL VASCULAR DISEASE, "NEURITIS," AND TABES DORSALIS

In September, 1931, a forty-seven-year-old surgeon began to suffer from fatigability and irritability. Although he had just returned from a summer vacation he found himself "all in" by noon of each day, even though he went to bed nightly as soon as he had had dinner and did not arise unduly early. At the same time he became aware of increasing irritability in his contacts, both familial and professional, and felt that he could not think clearly. In October, with the advent of colder weather, he commenced to suffer from coldness of the feet, particularly aggravated by the slightest drafts. This was so annoying that, in November, he consulted a physician, who considered peripheral vascular disease and premature cerebral arteriosclerosis to be

responsible. By February of the following year unsteadiness of the legs was evident. On walking any distance severe pain was felt in the calf muscles, and a "leathery" feeling developed in the feet and lower legs. Walking was particularly difficult on uneven ground, on stepping on and off curbstones, and on stairs. A particularly bad fall on the stairs led the sufferer to consult a neurologist, who found evidence of "neuritis" and because of this all the patient's teeth were extracted. By May his condition was so poor that he could no longer continue practicing surgery, and at this time he entered the hospital for study and treatment, approximately eight months after the onset of his difficulties.

Family and past histories were essentially irrelevant save for two facts. One year before the onset of the illness the patient's hair had turned gray rather suddenly. (*Premature graying* is a not uncommon story in patients with pernicious anemia.) One month before the onset of the illness there had been an acute, severe gastro-intestinal upset lasting for several days, following which intolerance to fatty foods had been noted.

Observations at examination were entirely normal save for the gray hair and the neurologic signs. There was no glossitis, no real pallor. The gait was ataxic, on a broad base, with Romberg's sign present. The ankle and patellar reflexes were absent. The sign of Babinski was not present. Incoordination was obvious in the performance of the heel-shin test. Strength of musculature was fairly well preserved. No abnormalities of superficial skin sensation to pin or brush were elicited. Position sense was markedly diminished in the toes and feet, and vibration sense was absent at the ankles and markedly diminished at the knees. No abnormalities were noted in the pupils or in the arms or trunk.

COMMENT.—*Tabes dorsalis*, so strongly suggested by the findings in the legs, is associated with some pupillary abnormalities (not necessarily Argyll Robertson pupils) in the overwhelming majority of cases. Peripheral neuritis of the type due to nutritional deficiency may, especially in chronic cases, resemble the condition in this patient. However, the absence of changes in superficial skin sensation and the minimal loss of motor power would be most unusual. Subacute combined degeneration of the spinal cord, associated with pernicious anemia, may, as in this case, assume a wholly tabetic form, although more commonly signs of pyramidal

tract damage (spasticity, sign of Babinski, and so on) are also present. In some instances signs are limited to the pyramidal tract. The differential diagnosis between parenchymatous neurosyphilis and the neural lesions of pernicious anemia may at times be impossible without examination of the spinal fluid. In the patient here presented it was felt that this procedure might well be delayed.

The absence of free hydrochloric acid in the gastric juice after the subcutaneous injection of 0.3 to 0.5 mg. of histamine phosphate is to be expected in 99 per cent of patients with subacute combined cord degeneration. It must be remembered, however, that about 15 per cent of all patients in the fifth, sixth, and seventh decades have posthistamine achlorhydria, so that, although the presence of free hydrochloric acid is presumptive evidence against this type of cord lesion, its absence is of little specific diagnostic significance.

Blood examination in this patient was as follows:

Red blood cells	3,240,000 per cu. mm.
White blood cells	4,400 per cu. mm.
Hemoglobin	73 per cent (11.4 gm. per 100 cc.)
Hematocrit	35.6 per cent
Mean corpuscular volume	109.8 cu. micra (normal 85 to 95 cu. micra)
Mean corpuscular hemoglobin concentration	32 per cent (normal 33 to 35 per cent)
Differential:	
Polymorphonuclear neutrophils	70 per cent
Small lymphocytes	25 per cent
Large lymphocytes	1 per cent
Monocytes	3 per cent
Basophils	1 per cent

There was more than normal variation in the size and shape of the red cells, some of which were polychromatophilic. Occasional microcytes, macrocytes, tail and pencil forms were seen. The platelets appeared moderately diminished.

Urine and stool examinations were normal.

The blood findings in this patient were entirely consistent with and, in fact, almost pathognomonic of pernicious ane-

responsible. By February of the following year unsteadiness of the legs was evident. On walking any distance severe pain was felt in the calf muscles, and a "leathery" feeling developed in the feet and lower legs. Walking was particularly difficult on uneven ground, on stepping on and off curbstones, and on stairs. A particularly bad fall on the stairs led the sufferer to consult a neurologist, who found evidence of "neuritis" and because of this all the patient's teeth were extracted. By May his condition was so poor that he could no longer continue practicing surgery, and at this time he entered the hospital for study and treatment, approximately eight months after the onset of his difficulties.

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brought about by the unremitting daily program of re-education in walking and coordination. Often these patients will fret at the slowness of progress and the tediousness of constant exercise and re-training. They will not infrequently balk at continuing, feeling that the outlook is unfavorable. They must constantly be encouraged and stimulated to keep everlastingly at their program of re-education. Without this, liver treatment may merely allow them to remain in status quo. It is indeed fortunate that today far fewer are similarly crippled because earlier diagnosis and treatment prevent the development of advanced lesions.

CASE III. PERNICIOUS ANEMIA IN SEVERE RELAPSE COMPLICATED BY URINARY TRACT INFECTION. UNTOWARD TRANSFUSION REACTION.

A housewife fifty-three years of age was admitted to the hospital complaining of weakness and anorexia. Eight months before admission, at a time when she considered herself in perfect health, she had had an acute gastro-intestinal upset following the eating of lobster. Although the episode lasted for only a few hours, she felt weak thereafter. Three months later there was a definite increase in weakness and a decrease in appetite. Three and a half months later, or approximately six weeks before admission, she suffered from a febrile illness lasting a fortnight, characterized by generalized aches and pains and low grade fever. Weakness was quite marked upon recovery from this episode, and pallor was observed for the first time. Her appetite decreased steadily, dyspnea appeared on exertion and a week before entry a canker on the tongue was noted which was painful. A total weight loss of 15 pounds had occurred.

The patient had never been a hearty meat eater; with her anorexia the ingestion of meat had been even further reduced. Her past history was uneventful except for an attack of renal colic a year before. There had never been any neurologic symptoms.

Examination showed a sallow, alert, active woman who looked older than her stated age. Sclerae were subicteric. The tongue was atrophic along the margins; on the under surface were two small (2 mm.) ulcerations. There was a rough, blowing systolic murmur heard all over the precordium, but otherwise the find-

mia. It should, however, be pointed out that this is not always the case. The errors in red cell counting have recently been discussed. Should the count here have been recorded at 3,740,000 (a value well within the range of unavoidable error) the color index would have been less than unity and the mean corpuscular volume 95 cu. m., a perfectly normal value. However, careful examination of the blood film would have shown the abnormalities noted and hence made the diagnosis more certain.

Treatment was begun by the intramuscular injection of the *dilute liver extract* which was then available. Ten cubic centimeters were given thrice weekly. (This material probably contained the equivalent of 1 U.S.P. injectable unit per cubic centimeter.) Within ten days the patient's general condition had improved markedly. He no longer had the constant feeling of weariness; his appetite, not previously thought to be poor, nevertheless improved. In a month the coldness in the feet had disappeared.

Shortly after the initiation of liver treatment, *physiotherapy* was commenced. In a fortnight the patient began systematic exercises and walking with the aid of crutches. With the advent of warm weather he was able to practice walking daily in a shallow swimming pool. By midsummer he could walk on dry land with the aid of two canes and in October, approximately five months after the beginning of treatment, he was able to return to work as an active surgeon. During this period, of course, he continued to have liver therapy, receiving the equivalent of 30 U.S.P. injectable units per week. Blood values reached a normal level within two months from the first treatment. During the next five years this patient continued to receive the equivalent of 30 U.S.P. injectable units weekly and thereafter 15 units weekly.

There are two important aspects of this case: first, the difficulties involved in diagnosis, largely arising because, in the absence of pronounced anemia, the correct diagnosis was not even considered; second, the recovery of essentially full neuromuscular function in a seriously crippled patient. This recovery could not have occurred had not liver treatment prevented further nerve degeneration, but was largely

jection of 0.5 gm. of caffeine sodium benzoate every two hours. Her condition remained critical throughout the night, although her temperature dropped to 104° F., pulse rate to 126, and respiratory rate to 36. At 3:00 A.M., after vomiting approximately 2000 cc. of dark brown fluid material, her temperature fell to 99.6° F. and she appeared moribund. The pulse was almost imperceptible at 112. Sixty cubic centimeters of 50 per cent glucose were given intravenously with definite improvement and lessening of signs of shock. This was followed by a constant intravenous infusion of 5 per cent glucose in normal saline.

Improvement continued although the course of recovery was stormy for the next four days with delirium, some vomiting and temperature as high as 102° F. Daily injections of 15 U.S.P. units of liver extract were given. A rise of reticulocytes to 11.6 per cent occurred five days after the first injection of liver extract and reached a peak value of 29.2 per cent two days later, when the patient became afebrile, mentally clear and free of nausea and vomiting. Ten days after the first liver injection the red cells numbered 2,060,000 per cubic millimeter; ten days later the red count was 3,070,000, hemoglobin 49 per cent (7.6 gm. per 100 cc.) and the patient was discharged from the hospital to be cared for by her family physician. During the last week mandelic acid given for her urinary tract infection resulted in satisfactory clearing of her urine.

COMMENT.—This patient obviously had pernicious anemia and a urinary tract infection. In spite of her low blood values she did not appear seriously ill on admission. However, within thirty-six hours, at a time before a response to liver therapy could have occurred, an acute exacerbation of her urinary infection rendered her condition critical. In spite of utmost care in the transfusing of blood a severe reaction occurred which almost cost the patient her life. The points to be emphasized are: first, the precarious balance in which the patient with untreated pernicious anemia in severe relapse exists and, second, the *dangers of transfusion* in dealing with such patients; although, as in this case, transfusion was a life-saving measure even though it almost resulted in immediate fatality. Adequate treatment a week or so earlier could have prevented the critical phase.

ings of the physical examination were normal. No abnormal neurologic signs were demonstrated.

Urine analysis showed moderate albuminuria and large numbers of white blood cells. Stools were normal. Blood nonprotein nitrogen was 42 mg. per 100 cc. Other blood examinations were:

Red blood cells	1,100,000 per cu. mm.
White blood cells	2,750 per cu. mm.
Hemoglobin	22 per cent (3.4 gm. per 100 cc.)
Hematocrit	12.1 per cent
Mean corpuscular volume	110 cu. micra
Mean corpuscular hemoglobin concentration	28.3 per cent
Icteric index	5
Reticulocytes	1.2 per cent

Differential:

Polymorphonuclear neutrophils	6 per cent
Eosinophils	6 per cent
Small lymphocytes	11 per cent
Large lymphocytes	0 per cent
Monocytes	7 per cent

The red blood cells varied markedly in size and shape, with large, oval macrocytes. The platelets were decreased in numbers.

On the morning following admission the patient received 30 U.S.P. units of liver extract intramuscularly. At that time, although she appeared weaker, her temperature was 99° F., pulse rate 100, respiratory rate 20. During the day, however, she had increasing frequency of urination, nausea and inability to take fluids by mouth. Her temperature rose to 102° F., pulse rate to 110.

By late afternoon the condition of this woman, who had walked into the hospital on the preceding day, was so poor that *blood transfusion* was deemed advisable. In an endeavor to avoid the untoward reactions so common after transfusions in pernicious anemia, only 300 cc. of carefully cross-matched blood from a compatible donor of her own blood group (Moss III) were given. An hour afterward she felt chilly and her oral temperature was 104.6°. Two hours after transfusion, the patient's rectal temperature was 107° F., pulse rate 140, respiratory rate 54. The blood pressure fell to 70 mm. Hg systolic and 40 mm. Hg diastolic. She was placed in shock position and given an in-

jection of 0.5 gm. of caffeine sodium benzoate every two hours. Her condition remained critical throughout the night, although her temperature dropped to 104° F., pulse rate to 126, and respiratory rate to 36. At 3:00 A.M., after vomiting approximately 2000 cc. of dark brown fluid material, her temperature fell to 99.6° F. and she appeared moribund. The pulse was almost imperceptible at 112. Sixty cubic centimeters of 50 per cent glucose were given intravenously with definite improvement and lessening of signs of shock. This was followed by a constant intravenous infusion of 5 per cent glucose in normal saline.

Improvement continued although the course of recovery was stormy for the next four days with delirium, some vomiting and temperature as high as 102° F. Daily injections of 15 U.S.P. units of liver extract were given. A rise of reticulocytes to 11.6 per cent occurred five days after the first injection of liver extract and reached a peak value of 29.2 per cent two days later, when the patient became afebrile, mentally clear and free of nausea and vomiting. Ten days after the first liver injection the red cells numbered 2,060,000 per cubic millimeter; ten days later the red count was 3,070,000, hemoglobin 49 per cent (7.6 gm. per 100 cc.) and the patient was discharged from the hospital to be cared for by her family physician. During the last week mandelic acid given for her urinary tract infection resulted in satisfactory clearing of her urine.

COMMENT.—This patient obviously had pernicious anemia and a urinary tract infection. In spite of her low blood values she did not appear seriously ill on admission. However, within thirty-six hours, at a time before a response to liver therapy could have occurred, an acute exacerbation of her urinary infection rendered her condition critical. In spite of utmost care in the transfusing of blood a severe reaction occurred which almost cost the patient her life. The points to be emphasized are: first, the precarious balance in which the patient with untreated pernicious anemia in severe relapse exists and, second, the *dangers of transfusion* in dealing with such patients; although, as in this case, transfusion was a life-saving measure even though it almost resulted in immediate fatality. Adequate treatment a week or so earlier could have prevented the critical phase.

CASE IV. "IDIOPATHIC" HYPOCHROMIC ANEMIA IN A MALE DUE TO SILENT GASTRIC TUMOR

This sixty-one-year-old salesman complained of pallor of some weeks' duration. His family history and past history were irrelevant save for the fact that a year previous he had been pale and tired for a period of several months but had recovered spontaneously. For about five weeks before being seen he had been aware of fatigability, pallor and cramps in his legs, especially at night. His appetite was good. Bowels were regular; no abnormal stool color had ever been noted. He had had no bleeding anywhere.

Examination showed a pale man with a smooth tongue which was not red. His fingernails were rather flat and broke easily. No other abnormalities were noted.

Urine and stool examinations were negative. No free hydrochloric acid was present in the gastric juice after histamine injection. Blood values were:

Red blood cells	4,320,000 per cu. mm.
White blood cells	7,500 per cu. mm.
Hemoglobin	42 per cent (6.5 gm. per 100 cc.)
Hematocrit	28 per cent
Mean corpuscular volume	64.8 cu. micra
Mean corpuscular hemoglobin concentration	23.3 per cent
Icteric index	2

Differential:

Polymorphonuclear neutrophils	68 per cent
Eosinophils	1 per cent
Small lymphocytes	21 per cent
Large lymphocytes	4 per cent
Monocytes	6 per cent

The red blood cells showed marked hypochromia; there was moderate variation in shape, all were small; the platelets were present in normal numbers.

Treatment was instituted with 0.3 gm. (5 grains) of ferrous sulfate three times daily after meals. Within a fortnight all symptoms had disappeared, the hemoglobin was 65 per cent and in two months it was 88 per cent, and the red cells numbered 5,080,000 per cubic millimeter. There were absolutely no symptoms. At this time gastro-intestinal x-ray examination was made

showing a filling defect on the lesser curvature of the stomach near the cardia. Several competent surgeons considered the lesion inoperable.

Eleven months later a routine check-up showed the hemoglobin to have fallen to 76 per cent. With re-institution of iron therapy it returned to 92 per cent in four weeks. Ten months later there was another relapse to 63 per cent, which again responded to iron. After this episode iron was continued indefinitely. Three years following this first examination symptoms referable to the stomach made their initial appearance; anemia did not recur, iron therapy being continued. Nine months later the patient succumbed with evidence of extensive malignant disease. During this period the hemoglobin never was below 88 per cent.

COMMENT.—This patient illustrates a point which cannot be emphasized too strongly: *Hypochromic anemia is almost always due to blood loss.* This may be physiologic (normal menses) or pathologic. When no history or obvious source of bleeding is found the gastro-intestinal tract must be investigated even though stool examinations are negative, there are no symptoms and the anemia has responded to treatment. Other lesions which may give rise to hypochromic anemia without producing local symptoms are diaphragmatic hernia, silent peptic ulcer, and benign and malignant tumors of the large bowel, especially those above the sigmoid. Hypochromic anemia should never be considered "idiopathic."

CASE V. SEVERE ANEMIA, SLIGHTLY MACROCYTIC, DUE TO HEMORRHAGE FROM A SILENT PEPTIC ULCER

A man of sixty-three years complained of progressive weakness and pallor. For at least four months mild pallor and fatigability had been noted. One week before he was seen he had fainted on arising in the morning. Since that time he had felt quite weak, had been noticeably paler, and had had mild anorexia. He had had no digestive disturbances, no pain, no melena.

The family and past histories were irrelevant. He had been remarkably free of illness all his life. Physical examination was normal except for marked pallor.

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This sixty-one-year-old salesman complained of pallor of some weeks' duration. His family history and past history were irrelevant save for the fact that a year previous he had been pale and tired for a period of several months but had recovered spontaneously. For about five weeks before being seen he had been aware of fatigability, pallor and cramps in his legs, especially at night. His appetite was good. Bowels were regular; no abnormal stool color had ever been noted. He had had no bleeding anywhere.

Examination showed a pale man with a smooth tongue which was not red. His fingernails were rather flat and broke easily. No other abnormalities were noted.

Urine and stool examinations were negative. No free hydrochloric acid was present in the gastric juice after histamine injection. Blood values were:

Red blood cells	4,320,000 per cu. mm.
White blood cells	7,500 per cu. mm.
Hemoglobin	42 per cent (65 gm. per 100 cc.)
Hematocrit	28 per cent
Mean corpuscular volume	64.8 cu. micra
Mean corpuscular hemoglobin concentration	23.3 per cent
Icteric index	2

Differential:

Polymorphonuclear neutrophils	68 per cent
Eosinophils	1 per cent
Small lymphocytes	21 per cent
Large lymphocytes	4 per cent
Monocytes	6 per cent

The red blood cells showed marked hypochromia; there was moderate variation in shape, all were small; the platelets were present in normal numbers.

Treatment was instituted with 0.3 gm. (5 grains) of ferrous sulfate three times daily after meals. Within a fortnight all symptoms had disappeared, the hemoglobin was 65 per cent and in two months it was 88 per cent, and the red cells numbered 5,080,000 per cubic millimeter. There were absolutely no symptoms. At this time gastro-intestinal x-ray examination was made

CASE VI. CONGENITAL HEMOLYTIC JAUNDICE FIRST MANIFEST AT THE AGE OF FORTY-FIVE AND MISTAKEN FOR PERNICIOUS ANEMIA

A forty-five-year-old poultryman complained of fatigability and pallor of six months' duration, coming on after an automobile accident in which he was tossed about but not otherwise injured. Three months after the onset of his symptoms a blood examination was reported to have shown 2,000,000 red blood cells and 50 per cent hemoglobin. One week following the intramuscular injection of a liver preparation the reticulocytes were reported to have been 20 per cent. After a month of continued liver therapy the red blood cells were said to have been 3,400,000 per cubic millimeter, but in spite of continued and even more intensive liver treatment the count had again fallen. The addition of iron had not been of benefit.

Family history indicated that the patient's mother, aged seventy-two, suffered from high blood pressure and gallstones with occasional bilious attacks associated with jaundice. His father died of Bright's disease at fifty-four years of age. One sister was living and well. Three children were all well.

At the age of twenty-five years the patient had had cystitis and had passed bloody urine. Ever since, he had had nocturia two to three times nightly. One year before being seen he had been operated upon for internal and external hemorrhoids. He had had severe bleeding. In the six months of his illness he had lost 12 pounds of which all but 2 had been regained.

Examination showed a pale, somewhat overweight man in no distress. The sclerae were faintly icteric. The apex impulse of the heart was just outside the midclavicular line. There was a loud apical systolic murmur. The rhythm was regular, the rate 104, the blood pressure in millimeters of mercury was 130 systolic and 60 diastolic. A firm sharp nontender liver edge was felt 6 cm. below the costal margin in the midclavicular line and a second mass, consistent in size and shape with the spleen, was felt 4 cm. below the costal margin in the left upper quadrant. Both masses moved with respiration. Pitting edema was present over both lower legs. Neurologic examination was negative.

The urine was *dark amber* with a *specific gravity* of 1.016. It contained no albumin, sugar or bile, and the sediment after centrifuging was negative. A positive test for urobilinogen was obtained in a 1 to 32 dilution. Stools were negative.

Urine and stool examinations gave normal values. Free hydrochloric acid was present in the gastric secretion.

Blood examination revealed:

Red blood cells	1,390,000 per cu. mm.
White blood cells	11,900 per cu. mm.
Hemoglobin	24 per cent (3.7 gm. per 100 cc.)
Hematocrit	14.2 per cent
Mean corpuscular volume	102.1 cu. micra
Mean corpuscular hemoglobin concentration	26.7 per cent
Icteric index	3
Reticulocytes	3.8 per cent

Differential:

Polymorphonuclear neutrophils	66 per cent
Band forms	14 per cent
Small lymphocytes	16 per cent
Large lymphocytes	2 per cent
Monocytes	2 per cent

There was moderate variation in the size and shape of the red blood cells, which appeared a trifle larger than normal. The platelets were normal.

COMMENT.—The high normal white blood cell count would be unusual in uncomplicated pernicious anemia, as would the relative increase in, and slight immaturity of, the polymorphonuclear cells. There were no true macrocytes nor were the platelets diminished. These findings, together with the free hydrochloric acid in the gastric juice, practically exclude pernicious anemia. The moderate increase in mean corpuscular volume is commonly found in many disorders involving the bone marrow. The only point suggesting the possibility of hemorrhage as a cause of the anemia was the episode of syncope followed by a marked increase in weakness and pallor. Roentgen examination of the gastro-intestinal tract was accordingly made, which showed a duodenal ulcer. With simple dietary measures and ferrous sulfate (4 grains three times daily by mouth after meals) the patient made an uneventful recovery. No ulcer symptoms were ever present.

Although there was no history of nocturnal paroxysmal hemoglobinuria, examination was made with benzidine reagent of each specimen passed during a twenty-four-hour period. No free hemoglobin was demonstrated. The negative Hinton reaction and the absence of a history of exacerbation of symptoms or of hemoglobinuria with exposure to cold practically excluded hemolytic anemia associated with the Donath-Landsteiner phenomenon. A conventional fragility test showed a trace of hemolysis in 0.85 salt solution, definite hemolysis in 0.80, and complete hemolysis in 0.34 salt solution.

The diagnosis of familial acholuric jaundice having thus been established, the patient was admitted to the hospital, transfused with 500 cc. of compatible citrated blood and on the following day splenectomy was performed (by Dr. Edward L. Young, Jr.). Blood examination immediately after operation showed 3,100,000 red blood cells per cubic millimeter and 70 per cent (10.9 gm. per 100 cc.) of hemoglobin. Convalescence was uneventful. Two weeks later the blood values were unaltered but the icteric index had fallen to 5 and the reticulocytes to 6 per cent. Ferrous sulfate (4 grains three times daily) was commenced.

The patient was discharged from the hospital and not seen again for a month at which time he was asymptomatic. The red blood cells numbered 4,010,000 per cubic millimeter, the hemoglobin 83 per cent (13.0 gm. per 100 cc.), the reticulocytes 3.2 per cent and the icteric index 5. Stained films no longer showed the large polychromatophilic cells but the small, deeply staining spherocytes characteristic of congenital hemolytic anemia were still present. These cells will continue, as will the abnormal fragility of the erythrocytes to hypotonic salt solution, although no recurrence of anemia is to be expected.

Blood examination showed: *

Red blood cells	2,060,000 per cu. mm.
White blood cells	10,100 per cu. mm.
Hemoglobin	55 per cent (8.6 gm. per 100 cc.)
Hematocrit	26.3 per cent
Mean corpuscular volume	127.7 cu. micra
Mean corpuscular hemoglobin concentration	32.9 per cent
Icteric index	25
Reticulocytes	24.7 per cent

Differential:

Polymorphonuclear neutrophils	72 per cent
Eosinophils	1 per cent
Small lymphocytes	20 per cent
Large lymphocytes	3 per cent
Monocytes	4 per cent

The stained blood films showed many small, darkly stained red cells, the characteristic "spherocytes" of familial acholuric jaundice. An almost equal number of the red cells were large and polychromatophilic. On the films stained with brilliant cresyl blue it was seen that practically all of these large cells contained reticulum, and represented cells recently released from the bone marrow. The platelets were normal.

COMMENT.—Splenomegaly, once considered common in pernicious anemia, is now rarely observed. This is no doubt due to the fact that patients with pernicious anemia can now be adequately treated in the first relapse and do not have the succession of remissions and relapses which once characterized the disease. In the past, splenomegaly was usually observed only after the disease had been active for a considerable period of time. The increased numbers of reticulocytes noted one week after the beginning of liver therapy had been wrongly interpreted as a specific response to treatment. No doubt a reticulocyte count *before treatment* would have been as high. The apparent improvement in blood values was the result of a spontaneous fluctuation rather than a response to treatment. Anemia, with an elevated icteric index and constant reticulocytosis, is generally hemolytic in origin.

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TREATMENT OF PERIPHERAL VASCULAR DISEASES

JOHN HOMANS, M.D.*

ARTERIOSCLEROTIC ARTERIAL DEFICIENCY

THE disease shows itself mainly in the legs. It affects persons beyond the age of fifty-five and both sexes about equally. Among diabetics it appears about five years earlier than in others.

Pathology.—There is hardening of both large and medium-sized arteries by arteriosclerosis. The arterial narrowing, which is patchy as a result of mural thrombi, causes a varying degree of ill nourishment as between the two limbs and between terminal parts, muscles and skin. Occlusive thrombosis, when added, slowly or rapidly leads to ulceration and gangrene. The tissues show little resistance to infection.

Symptoms.—1. Premonitory symptoms and signs are coldness and pallor of the feet and lower legs, moderate atrophy of the soft parts and intermittent claudication.

2. The symptoms of the more advanced stage are redness or cyanosis of toes and forefoot on dependency; spontaneous pain in discolored parts, aggravated by elevation; ulceration and gangrene in small areas beside deformed nails or over bony prominences of the toes, especially beside the great toenail and over the first metatarsophalangeal joint.

3. In the advanced stage gangrene spreads to the foot, with infection of the small bones and joints of the toes. Sepsis is increasingly dangerous, especially in diabetics. Sudden femoral arterial occlusion causes widespread, purplish discoloration, coldness and pain, much as in arterial embolism. Moist gangrene and gas bacillus infection then threaten.

Course.—Deterioration is usually gradual and marked only by minor gangrene unless a large vessel becomes rapidly occluded, threatening loss of a limb.

* Clinical Professor of Surgery, Tufts College Medical School; Consultant in Surgery, Peter Bent Brigham Hospital.

Diagnosis.—Diagnosis depends on the advanced age of the patient, a clinical history as above, coldness of the feet and lower legs to the touch, and disappearance or weakening of the peripheral pulses. The toes of one or both feet become pale on elevation to 30 to 45 degrees for two minutes (any retention of pinkness is a favorable sign).

Treatment

PREMONITORY AND EARLY STAGES.—In the premonitory stages heat is conserved by wearing woolen socks or stockings in cold weather, both day and night. Shoes should be loose and comfortable. If exposure to cold is unavoidable, footwear should be as follows: woolen socks, a fleece- or felt-lined slipper, and a loosely fitting waterproof shoe or arctic. Locomotion should be calculated as to speed and distance to avoid bringing on the limp. Smoking should be abandoned.

Buerger-Allen exercises will improve warmth and locomotion. *Period I:* Elevation at 30 degrees must be long enough (usually one or two minutes) to secure pallor. *Period II:* Depression of the legs as the patient sits on the edge of the bed or couch should be maintained for about two minutes, or long enough to secure a pink flush. Toes and feet are alternately flexed and extended, pronated and supinated, adducted and abducted. *Period III:* To complete the cycle, the legs are placed in a horizontal position, wrapped in a warm blanket. Each cycle, requiring six to seven minutes, is to be repeated four or five times during a half hour; each half-hour's block of cycles is to be carried out three times a day. Persistence in this treatment is likely to produce as much reactive hyperemia and collateral circulation as the most elaborate and expensive apparatus, which should be reserved for combating the painful states of a more advanced disease, especially in the cases of individuals who find that the Buerger exercises require too much exertion.

The Toilet of the Feet.—After a daily cleansing of the feet in warm water, the skin is dried and then greased with lanolin. Before the nails are cut or filed, the feet should be soaked for half an hour. Unless dermatophytosis is present, the nails should be cut square and rather long to prevent

lateral curving and growing into the flesh. Cotton may be pressed under the terminal edge of ingrowing nails. Calluses are best kept down with sandpaper, and corns should be cut only by an expert, or treated with salicylated collodion. *Dermatophytosis* beneath the nails leaves an accumulation of detritus, causing a lateral curvature and deep indentation by the edge of the nail. For both this and the cutaneous form, the toes should be soaked for half an hour at bedtime in a dilute solution of chlorinated soda (liquor sodae chlorinatae, about 2 tablespoonfuls to a quart of warm water, to make the solution slightly soapy to the touch), or potassium permanganate, 1:3000. After softening, clip back the nails and gently scrape out the detritus. Then apply overnight a fungicide ointment such as Whitfield's or one of the proprietary varieties containing salicylic acid, benzoic acid and thymol. Soaks and applications of ointment may be used for four nights out of a week over a period of three out of four weeks and a block of treatments repeated as seems to be needed.

ADVANCED STAGES.—Treatment of the more advanced, painful states of this disease should be carried out as outlined above and will usually require rest in bed as well. Pain is poorly controlled by drugs. Morphine is contraindicated. Vasodilating drugs act only temporarily and none is more effective than a good-sized alcoholic drink, especially useful when taken before retiring. Aspirin, 5 to 10 grains, perhaps combined with codeine sulfate, $\frac{1}{2}$ grain, is helpful. Since an elevated or level position of the leg usually increases pain, an optimum position of slight dependency should be sought, especially for the night, not such a position as will cause edema but which will permit arterial blood easy access to the feet. Buerger-Allen exercises will often relieve pain. If not, the suction and pressure boot or intermittent venous hyperemia may be substituted with success.

Gangrene.—Gangrene of the dry, mummifying type should always be treated conservatively. The patient is confined to bed and the legs and lower body are covered with a large cradle warmed to about 80° F. The gangrenous part is treated like an open wound, sponged off daily with a sterile cotton swab wet in aqueous Zephiran (1:1000) or freshly diluted

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DIABETIC GANGRENE

Gangrene occurs in late middle to advanced age, about equally in the sexes, and under two sorts of conditions, namely: those due primarily to arteriosclerosis (about five years earlier than in nondiabetics) and those due primarily to infection.

Conditions Due Primarily to Arteriosclerosis

These are characterized by the following symptoms and signs:

1. Absent or feeble pulsations in the peripheral arteries of the legs.
2. A cold foot, blanching on elevation; red or dusky, and shiny on dependency.
3. Association of gangrene with any necrosis of bone which may be present.
4. Pain more severe than the local lesion appears to warrant.
5. Gangrene as the presenting lesion, if any.

TREATMENT.—The same prophylactic care as for arteriosclerotic arterial deficiency (*q.v.*) in nondiabetics, especially of deformed toenails, corns, calluses and dermatophytosis.

Treatment of gangrene or ulceration calls for rest in bed, a cradle warmed to about 80° F., sterile coverings and aseptic dressings as for nondiabetic arterial deficiency. In addition, control of diabetes by the administration of insulin is required, but unusual aggravation of diabetes will not occur unless infection is added. The injunction against local removal or amputation of a gangrenous part is absolute, and deformed nails should never be avulsed because of the danger of introducing and spreading necrosis and gangrene. Any area of necrosis or ulceration due to a deformed toenail should be treated by gently elevating the edge of the nail upon vaseline gauze, gutta percha tissue, or cellophane. For open ulceration continuous warm saline or boric acid fomentations should be used during the acute stage, and, later, antiseptic washes and aseptic vaseline gauze or 10 to 20 per cent sulfathiazole ointment dressings as in arteriosclerotic states.

Lugol's solution (1:200) in water, and covered with a sterile vaseline gauze dressing. Though separation of the gangrenous area may require many months, the natural process is preferable to surgical removal, which usually causes a spread of gangrene and infection and is seldom indicated. A narrow, reddened area proximal to a line of demarcation is a reassuring sign. If an ulcer or an open cavity is present after gangrenous material has been cast off, it may be buttered with a 10 to 20 per cent sulfathiazole ointment or kept filled with a chlorine-delivering antiseptic such as azochloramide (a tablet to a quart of saline solution) or Eusol (mixed equal parts with liquid petrolatum). Neither causes pain and both promote healing. For cavities lined with heavy sloughs, crystals of urea freely dusted in are excellent. The formula for *Eusol* is:

Chlorinated lime	12.5 gm.
Boric acid	12.5 gm.
Distilled water	1000 cc.

Allow to stand twelve hours and filter. Store in a dark bottle.

Lymphangitis or Spreading Cellulitis.—The appearance, in spite of such treatment, of lymphangitis or a spreading cellulitis is an indication for surgery (see also under Diabetic Gangrene), usually a guillotine amputation through the calf or lower thigh.

Determination of the Level of Amputation.—Two methods are used. 1. A *histamine wheal* is made by placing a drop of histamine acid phosphate (1:1000) upon the clean, dry skin of the leg. After needling the skin several times through the drop, the examiner feels for the wheal with the finger tip. Failure of the wheal to appear in three to five minutes indicates a serious ischemia. In a series of wheals made from mid-thigh to foot, the lowest acceptable wheal indicates the level at which amputation may be performed.

2. A *saline wheal* (McClure-Aldrich test) is made by injecting intradermally 0.1 cc. of physiologic salt solution into the leg. The wheal should last for the better part of an hour. An early disappearance has the same prognostic significance as the failure of the histamine wheal.

chemotherapy can be adjusted. For the usual streptococcal infection, give sulfanilamide in a dosage of 4 gm. divided over the first four hours, to be followed by 1 gm. every four hours. For a streptococcal or mixed infection, sulfadiazine in similar dosage is efficacious. Since concentration of the drug in the blood (8 to 10 mg. per cent) is an objective, the intake of fluid should be kept at about 2500 cc. During the period of emergency, toxic manifestations may practically be ignored. Intolerance to sulfanilamide is unlikely before a week or ten days have elapsed. It is marked by a low white cell count, unexplained fever, or a skin rash. Diminution of the urinary output is an early sign of intolerance to sulfadiazine. For a staphylococcal infection, sulfathiazole is appropriate. The dosage and evidences of overdose are similar to those of sulfadiazine.

When coma, nausea, or vomiting contraindicates the administration of the sulfonamides by mouth, they may be given intravenously in the form of their sodium salts, 4 gm. to 1000 cc.

Indications for Amputation.—An initial twelve-hour period of observation of the patient with diabetic gangrene is permissible and even advisable. Following this, if the blood culture is positive, the diabetes clearly difficult to control, and the local lesion worse or no better, an emergency amputation is indicated. If progress is favorable, if cellulitis and lymphangitis are not extending, observation should be extended for twelve hours more.

Twenty-four hours after the initiation of treatment, the diabetic's blood chemistry should be on the way to adjustment and his fluid balance, by venoclysis if necessary, made normal. If, on the other hand, infection and diabetes are not controlled, an emergency amputation is indicated.

THROMBO-ANGIITIS OBLITERANS (BUERGER'S DISEASE)

The disease occurs in males, during young adult life and through middle age, and is almost unknown in females. It affects any race, but especially Jews, and only very rarely the American Negro.

Conditions Due Primarily to Infection

These are characterized by the following symptoms and signs:

1. Normal or moderately diminished pulsations in the peripheral arteries of the legs.
2. Warmth of the foot and leg (distinguish from the heat of inflammation).
3. Necrosis and infection of toe joints and bony structures without gangrene.
4. Pain absent or much less than the local condition of infection might be expected to cause.
5. Gangrene only when it follows infection.

TREATMENT.—Minor infections not associated with cellulitis or lymphangitis require rest in bed and a protective, warmed cradle. A runaround, or such an infection as that beside a deformed nail or under a callus or bunion, which does not subside promptly under warm fomentations should be treated by the gentlest possible incision made under a low spinal anesthesia, or even a light inhalation anesthesia, but never under local infiltration. Continuous wet, warm saline or boric acid fomentations should then be continued.

Emergency treatment is required by more serious infections, especially if cellulitis and lymphangitis are present. Even without chills and high fever, invasion of the blood stream is probable. Medical and surgical opinion and treatment should be combined.

Lesions not obviously requiring drainage, such as an inflamed callus or bunion, an infected interphalangeal joint, or runaround, should be treated by immobilization and by warm, moist fomentations of saline or boric acid solution. Infections requiring drainage, such as osteomyelitis of a phalanx or supuration beneath a callus, in a joint or in a tendon sheath, should be incised, and at the same time blood secured for culture together with a study of the blood sugar and carbon dioxide combining power. A smear and culture from the local lesion should also be made.

Use of Sulfonamides.—One of the sulfonamides should at once be administered. When the bacteriology is known,

chemotherapy can be adjusted. For the usual streptococcal infection, give sulfanilamide in a dosage of 4 gm. divided over the first four hours, to be followed by 1 gm. every four hours. For a streptococcal or mixed infection, sulfadiazine in similar dosage is efficacious. Since concentration of the drug in the blood (8 to 10 mg. per cent) is an objective, the intake of fluid should be kept at about 2500 cc. During the period of emergency, toxic manifestations may practically be ignored. Intolerance to sulfanilamide is unlikely before a week or ten days have elapsed. It is marked by a low white cell count, unexplained fever, or a skin rash. Diminution of the urinary output is an early sign of intolerance to sulfadiazine. For a staphylococcal infection, sulfathiazole is appropriate. The dosage and evidences of overdose are similar to those of sulfadiazine.

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The disease occurs in males, during young adult life and through middle age, and is almost unknown in females. It affects any race, but especially Jews, and only very rarely the American Negro.

Etiology.—The *etiology* is obscure, but the dermatophytoses (fungus infections) are significantly related and tobacco-smoking is at least a serious aggravating factor.

Pathology.—A chronic, or subacute, recurrent granulomatous process attacks the blood vessel wall, causing thrombosis in the large, medium-sized and small arteries and veins of the legs (rarely in the arms). There is obstruction or extreme narrowing of the vessels involved. The peripheral arterial circulation is greatly slowed and restricted, being carried on by fine, numerous collateral vessels. A wandering superficial thrombophlebitis is common.

Clinical Course.—Intermittent claudication covers a period of months or years, more pronounced in one leg than the other and without spontaneous pain. The feet are susceptible to cold, but their appearance is not remarkable. The peripheral pulses are absent or feeble on one or both sides. Injury often precipitates the onset of the disease. Its advance is marked by rubor, increased coldness, and spontaneous pain, aggravated when gangrene involves the toes. Gangrene (dry type) is usually limited to the tip of one or more toes or a small area beside a toenail. Edema is apt to appear, increasing the malnutrition and pain. Infection is not at first serious. Later, local joints and tendon sheaths are involved. The disease comes in waves and may remain stationary for months or years if serious destruction can be avoided. Pain and infection, rather than extensive gangrene, usually enforce amputation.

Diagnosis.—The diagnosis is suggested by a history of intermittent claudication in a patient under fifty-five years of age, usually between twenty and forty at the onset. A loss of the peripheral pulses, first in one foot, is noted. Later, coldness, rubor on depression and finally spontaneous pain appear. No adequate distinction from arteriosclerosis is possible in late middle age except by lack of arterial calcification in Buerger's disease.

Treatment

EARLY STAGE OF THE DISEASE.—In the early stage *absolute withdrawal of tobacco* is essential, no compromise being

allowable. Even inhalation of denicotinized tobacco (if such exists) may be harmful. Warning should be given that the resulting improvement in locomotion and lessening of any rubor present may not be apparent for four months or more.

Buerger-Allen exercises (p. 1458) are especially useful, since the patients are young enough to be capable of developing a collateral circulation. Each block of individual cycles should occupy a half hour and should be carried out three times a day.

Dermatophytosis requires special care. This disease will often be found not only beneath the nails and between the toes but upon the foot itself. The feet should be soaked daily for half an hour in a warm chlorinated soda solution—liquor sodae chlorinatae or its equivalent—about 2 tablespoonfuls to the quart or sufficient to make the solution soapy to the touch. Permanganate of potash, 1:3000, may be used, or 1 per cent thymol in 50 per cent alcohol. Beside their fungicidal action, the solutions soften the nails, so that these can be clipped back, permitting the thickened skin and detritus to be scraped away. Then fungicide ointments or liquids can be applied with a greater prospect of success. No exact prescriptions are recommended but a salicylic-benzoic acid combination with thymol (if not too irritating) is as universally useful as any. Some proprietary preparations are good. To avoid overtreatment, the soaks may be used for four nights out of a week and omitted for three, the treatment continued for several weeks, then omitted for a week to study the effect.

Protection from cold and from injury is important. Shoes should be loose and comfortable. In cold weather woolen socks must be worn at night as well as during the day, and since cooling any part causes general vasoconstriction, the hands as well as the feet must be protected. A woolen night-cap is not to be despised. Exercise should be taken, to counteract muscular atrophy, up to the point of exciting the numb pain of the intermittent limp. Under treatment, pace and distance should improve.

THE ADVANCED DISEASE (*Pain, Rubor, Ulceration*).—Confinement to bed is required. A large cradle, warmed to about 80° F., should cover feet, thighs and lower body. Since ele-

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Treatment

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bosed femoral artery may be useful. Blocking the sensory nerves supplying the foot through surgical incisions is a neat, anatomical means of relieving pain.

9. *Prophylactic removal of toes and toenails.* In an interval between attacks, as when sympathectomy has caused the foot to become warm and improved in color, stiff, useless, bloodless toes, especially when badly infected with fungus, may be amputated by the expert.

ADVANCED DISEASE ACCOMPANIED BY INFECTION.—Infection occasionally attacks joints, tendon sheaths and the fascial spaces of the foot. Even then, the condition may be treated successfully by the removal of infected, devitalized tissue so that perfect, open drainage can be secured.

In default of securing a useful foot, especially when infection threatens the patient's life, the leg should be amputated, rarely if ever below the knee joint, usually through the knee.

THE ARTERIAL VASOCONSTRICTIONS AND VASOSPASMS

These include a large group of conditions marked by continued vasoconstrictions, by intermittent or acute vasospasms, and by combinations of the two. With the continued vasoconstrictions, the hands and feet are chronically bluish-red and moist (*acrocyanosis*; *livedo reticularis*; *erythrocyanosis frigida*). With the recurrent, acute vasospasms, the hands and feet are reasonably normal in color but subject to digital vasospasm (*Raynaud's disease*). In the mixed type the extremities are blue and red, and subject to acute vasospasm in response to cold (by some authors, *Raynaud's disease*; by others, *acrocyanosis*, with an exaggerated reaction to cold). All such states represent sympathetic dysfunctions. There are also embolic, traumatic and perhaps infectious arterial constrictions.

Raynaud's Disease

In its typical form Raynaud's disease is rare, and is principally confined to youngish females. There is often an emotional background.

vation increases pain, the patient desires to hang the foot out of bed, causing edema, which in turn interferes with the circulation in the toes. To overcome pain and secure maximal vasodilatation are therefore the first considerations.

1. *Abstinence from smoking* is vital and alone may relieve pain.

2. Successful treatment of *dermatophytosis* (already discussed) may relieve pain.

3. *Attractive food and surroundings*, with mental distractions, aid by lessening attention to pain.

4. *Dressings*. After cleansing between the toes and about the nails with cotton swabs wet in Zephiran (1:1000) or a watery dilution of Lugol's solution (1:200), the parts should be dried; sterile vaseline gauze or 10 to 20 per cent sulfathiazole ointment is applied to any ulcerated surfaces and films of cotton are placed between the toes. The foot should then be covered with a sterile towel, loosely pinned about it.

5. *Drugs*. Morphine must be avoided because of its habit-forming quality. In any case, it rapidly loses its effectiveness. For really serious pain, drugs are valueless. Aspirin, perhaps combined with codeine, is as useful as anything. A good drink of alcohol at night often assuages pain and favors sleep.

6. *Intravenous hypertonic saline solution*. Three hundred cc. of a 3 per cent solution of sodium chloride slowly given, intravenously, three times a week for several weeks may be helpful and can scarcely do harm.

7. In the absence of infection more serious than a local sore or area of gangrene upon one or more toes, the use of the suction and pressure boot, of intermittent venous hyperemia, or of the tipping bed (if available) is safe and may prove helpful. In unexpected (and unexplained) instances, such means of raising capillary pressure may relieve pain. These methods are certainly of no such value that they should be secured at burdensome expense to the patient.

8. *Early surgical relief*, especially lumbar sympathectomy, is indicated in difficult cases, even if preliminary procaine block shows that little or no vasodilatation is possible. Periarterial sympathectomy (femoral) or resection of the throm-

bosed femoral artery may be useful. Blocking the sensory nerves supplying the foot through surgical incisions is a neat, anatomical means of relieving pain.

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These include a large group of conditions marked by continued vasoconstrictions, by intermittent or acute vasospasms, and by combinations of the two. With the continued vasoconstrictions, the hands and feet are chronically bluish-red and moist (*acrocyanosis*; *livedo reticularis*; *erythrocyanosis frigida*). With the recurrent, acute vasospasms, the hands and feet are reasonably normal in color but subject to digital vasospasm (*Raynaud's disease*). In the mixed type the extremities are blue and red, and subject to acute vasospasm in response to cold (by some authors, *Raynaud's disease*; by others, *acrocyanosis*, with an exaggerated reaction to cold). All such states represent sympathetic dysfunctions. There are also embolic, traumatic and perhaps infectious arterial constrictions.

Raynaud's Disease

In its typical form Raynaud's disease is rare, and is principally confined to youngish females. There is often an emotional background.

Pathology.—Spasm of digital arteries occurs, at first without organic change, but later with sclerosis and permanent narrowing of these vessels.

Course.—At an early stage the hands appear normal, but on exposure to cold or emotional excitement the fingers are subject to attacks of deep cyanosis (asphyxia) or even ivory whiteness (ischemia). The fingers are principally affected (toes less so). Later, after years of repeated attacks, the fingers become sclerosed, tapered, and subject to small painful sores at their tips.

TREATMENT.—Treatment is palliative only, except for sympathectomy. The hands must be protected from cold by woolen or fur coverings. Emotional stress is to be avoided. The patient must sleep in a warm room and should begin the day in cold weather by warming her hands in hot water; then she should dry the fingers and rub in cold cream or lanolin. In the late stages precautions should be intensified, surgical treatment then being useless. Sympathectomy, of the preganglionic type, must be performed early to be successful. It is especially required for outspoken cases and for persons whose occupation prevents their taking ordinary precautions.

Acrocyanosis and Allied States

ACROCYANOSIS.—This disease is marked by reddish to bluish hands and feet, without edema but often with serious hyperidrosis, making social and professional contacts embarrassing. The simplest form, marked by evenly distributed color, is intensified by exposure to cold. Either the hands or feet may be most seriously affected. Ulcerations do not occur.

Treatment.—Except for avoiding exposure to cold, there is no nonsurgical treatment. Hyperidrosis is principally influenced by emotional stimuli, especially embarrassment. Sympathectomy (preganglionic type) is curative.

ERYTHROCYANOSIS FRIGIDA; PERNIO.—This more serious form is marked by the appearance, above the ankles and more on the back of the calves than the front, of round or elongated indurated areas which break down into ulcers. Both extremities are cyanotic but the ulcers occur on the legs. The indurations, red at first, change to purple before breaking

down to shallow ulcers. The disease is to be distinguished from erythema induratum (Bazin's disease), a tuberculid which occurs on the legs of ill-nourished girls without any background of cyanosis.

The disorder is confined to girls and young women. Induration and ulceration begin with cold weather and heal in the spring, leaving purple scars. The disease lasts many years, perhaps indefinitely, with remissions.

Treatment.—Protection from cold, even going to bed for the winter, does not necessarily prevent ulceration. There is no palliative treatment. Lumbar sympathectomy (bilateral) is of great benefit and should be permanently curative.

LIVIDO RETICULARIS (Racemosa, Annularis; Cutis Marmorata).—Instead of being a solid red or purple color, the limbs are covered with cyanotic blotches, imperfect rings, or arborizations. The change usually involves the feet and lower legs but often extends to the thighs and occupies the hands and arms as well. The limbs are cold and moist, most so in cold weather.

The disorder is one of youth to middle age and occurs in both sexes about equally.

Course.—The disease may appear first in one leg and then advance slowly in all limbs. Ulceration is rare but may develop into gangrene of the toes and feet. Amputation may even be required.

Treatment.—No palliative treatment is of any value. Lumbar sympathectomy changes the purple patches to pink but does not obliterate them; thus it is of great benefit, though not curative. The benefit of sympathectomy is predicted by the effect of a sympathetic procaine block.

Scalenus Syndrome: Arteriospasm Related to Cervical or First Rib

Arterial spasm with or without thrombosis is less common than nervous disorders due to pinching of the lower cord of the brachial plexus behind the scalenus anticus muscle. Very much the same thing may occur whether or not a cervical rib is present.

Youngish to middle-aged persons of either sex are affected, especially if they work with arms at their sides.

Pathology.—Spasm of digital arteries occurs, at first without organic change, but later with sclerosis and permanent narrowing of these vessels.

Course.—At an early stage the hands appear normal, but on exposure to cold or emotional excitement the fingers are subject to attacks of deep cyanosis (asphyxia) or even ivory whiteness (ischemia). The fingers are principally affected (toes less so). Later, after years of repeated attacks, the fingers become sclerosed, tapered, and subject to small painful sores at their tips.

TREATMENT.—Treatment is palliative only, except for sympathectomy. The hands must be protected from cold by woolen or fur coverings. Emotional stress is to be avoided. The patient must sleep in a warm room and should begin the day in cold weather by warming her hands in hot water; then she should dry the fingers and rub in cold cream or lanolin. In the late stages precautions should be intensified, surgical treatment then being useless. Sympathectomy, of the preganglionic type, must be performed early to be successful. It is especially required for outspoken cases and for persons whose occupation prevents their taking ordinary precautions.

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Treatment.—Except for avoiding exposure to cold, there is no nonsurgical treatment. Hyperidrosis is principally influenced by emotional stimuli, especially embarrassment. Sympathectomy (preganglionic type) is curative.

ERYTHROCYANOSIS FRIGIDA; PERPIO.—This more serious form is marked by the appearance, above the ankles and more on the back of the calves than the front, of round or elongated indurated areas which break down into ulcers. Both extremities are cyanotic but the ulcers occur on the legs. The indurations, red at first, change to purple before breaking

spasm is relaxed and the collaterals are opened. This is especially true of the brachial artery just above the elbow. Warmth and gentle massage may assist in relieving the spasm. Papaverine hydrochloride in $\frac{1}{2}$ -grain dosage may be given and repeated in two hours. A sympathetic block, thoracic or lumbar as the case may be, though theoretically valuable, has little or no effect upon the local area of spasm but should aid in developing a collateral circulation.

ARTERIAL EMBOLISM

Differential Diagnosis

It is not easy to distinguish between arterial embolism, sudden arterial thrombosis, and arterial spasm associated with the onset of the inflammatory type of thrombophlebitis. In these three states, the femoral artery is far more often involved than any other.

A comparison of the features of the three conditions follows:

1. *Arterial Embolism*.—There is a background of organic heart disease, especially auricular fibrillation, in patients of any age. The onset is often marked by premonitory coldness and numbness before ischemia and agonizing pain set in. Vigorous pulsations are often transmitted by an embolus in the common femoral, but none are felt beyond. The foot is cyanotic to purple, the leg cold.

2. *Arterial Thrombosis*.—There is a background of arteriosclerosis in elderly persons usually with previous evidence of arterial deficiency in one or both feet. The onset varies in suddenness much as does arterial embolism. Good or poor pulsations are present in the common femoral, none beyond. The leg is cold; the foot cyanotic or purple.

3. *Arterial Spasm with Femoro-iliac Thrombophlebitis*.—Individuals of any age, confined to bed by disease, injury, or operation are affected. The onset is sudden, with a variable degree of pain, which only rarely is severe. The whole leg is at first cold, numb, white, but not swollen or cyanotic. The femoral pulsations are absent or very feeble. Tenderness over the femoral vessels at the groin is present. Peripheral

Pathology.—The subclavian artery is rarely thrown into spasm where it passes over the rib. More often the subclavian is dilated and the brachial is constricted, due perhaps to irritation of vasoconstrictor fibers in the lower cord of the brachial plexus as it passes over the rib.

Symptoms.—The fingers and hand become cold and numb. The radial pulse may disappear.

Diagnosis.—A thickened or dilated subclavian artery may be felt above the clavicle. A lump may be felt in the brachial, beyond which no pulse is palpable. The x-ray may or may not show a cervical rib.

Treatment.—The treatment is surgical. Release of the subclavian artery and brachial plexus by dividing the tendon of the scalenus anticus muscle may or may not cure. A contracted (thrombosed) artery should be resected.

Traumatic Arterial Spasm

The large artery of any limb may be thrown into spasm by a variety of injuries, some of which seem trivial. Most commonly, bullet wounds and fractures (supracondylar) at the elbow are responsible, but even a needle thrust too deeply into the antecubital space in making a venipuncture may excite spasm.

The lesion may occur at any age but is seen most often in children (Volkmann's contracture).

Pathology.—The passage of a bullet or needle near an artery or the bruise of a bony fragment causes the artery to contract violently. A little blood still passes through it and local spasm may end in total closure or in rapid or slow relaxation. The state of bloodlessness, coldness and loss of peripheral pulsations in the limb indicate the severity of the accident.

Course.—Unless spasm rapidly relaxes, the peripheral part undergoes a slow deforming ischemic contracture or some degree of gangrene.

Treatment.—What is done to the limb itself in the line of loosening splints, relaxing joints and similar measures has little influence. The artery should be explored and if extensively constricted it should be resected. In this way, peripheral vaso-

spasm is relaxed and the collaterals are opened. This is especially true of the brachial artery just above the elbow. Warmth and gentle massage may assist in relieving the spasm. Papaverine hydrochloride in $\frac{1}{2}$ -grain dosage may be given and repeated in two hours. A sympathetic block, thoracic or lumbar as the case may be, though theoretically valuable, has little or no effect upon the local area of spasm but should aid in developing a collateral circulation.

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pulsations are absent. (See Thrombophlebitis, Inflammatory Type.)

Location or Level

In the lower limb, the embolus lodges in the external iliac or common femoral artery, rarely the popliteal; occasionally, at the iliac bifurcation. The level is recognized by color, coldness and the pulsations. Gangrene of the lower leg is common.

In the upper limb, the embolus usually lodges in the axillary or brachial artery. The result is less serious than in the leg. The hand is cold and numb; the fingers contracted, and white to cyanotic in color. Serious gangrene of the fingers is uncommon.

Treatment

Early *embolectomy*, within four to six hours, is the procedure of choice. The use of *heparin*, by preventing secondary thrombosis, prolongs the preoperative period. Therefore, if heparin is given (see under Thrombosis of the Deep Veins), successful embolectomy may be carried out even twenty-four hours after lodgment. Heparin alone, if means of operating are not at hand, is often helpful, preventing secondary thrombosis.

Papaverine hydrochloride may be given in a dosage of $\frac{1}{2}$ grain and repeated in two hours to relax peripheral spasm and encourage a collateral circulation. Sympathetic procaine block should be used.

The body and lower limbs should be warmed under a cradle at about 80° F. to encourage vasodilatation. The limb itself should be wrapped in cotton or wool (to prevent loss of heat) and subjected to no direct heat of over 80° F. The suction and pressure boot may aid in developing a collateral circulation.

THROMBOSIS OF THE DEEP VEINS

Two kinds of thrombosis occur in the deep veins: a quiet thrombosis, *phlebothrombosis*, and an outspoken, inflammatory thrombosis, *thrombophlebitis*. The quiet sort causes little

venous obstruction but is a source of easily detached *pulmonary emboli*. The outspoken thrombophlebitis causes venous obstruction and swelling of the limb, *phlegmasia alba dolens*, but almost no pulmonary embolism.

Quiet Thrombosis (Phlebothrombosis)

This form occurs as a complication of serious illness, operation and injury, usually in middle and advanced ages, but sometimes in young adult life. The onset is usually early after confinement to bed, being favored by an enfeebled circulation and the sitting or reclining position. The condition occurs occasionally in active life.

Pathology and Course.—Beginning in the venous plexuses of the calf and foot, the soft, clotlike process progresses in a sluggish current, tending to organize and heal on meeting an active stream, but it may form, unpredictably, a propagating thrombus in the femoral vein. This thrombus may adhere loosely, growing up into the common femoral and iliac veins, whence small fragments may repeatedly break off; or the floating thrombus may become a huge, fatal pulmonary embolus. A large embolus, giving little or no warning, usually comes from low in the leg. Small, repeated infarctions usually come from a partly adherent thrombus in the upper femoral or external iliac vein.

Symptoms and Signs.—Often there is no pain, or only moderate pain, in the calf. Swelling is absent or slight. Blueness of the foot is absent, or slight on depression. Elevation for several days often deceptively seems to bring complete relief. Discomfort in the back of the calf on forced dorsiflexion of the foot, the *dorsiflexion sign*, is almost always present. Some degree of fullness, tenderness and tension of the calf muscles is rather common.

Pulmonary infarcts, if small, cause pleuritic pain, perhaps cough and bloody expectoration; if large, substernal agonizing pain, resembling coronary infarction, with labored breathing.

TREATMENT.—Thrombosis is less likely to occur if the legs can be exercised during life in bed rather than left relaxed and dependent. Slight elevation (4 inches) of the foot

of the bed and free exercise of the legs, with or without nursing aid, oppose thrombosis. Deep breathing, relief of abdominal distention, and adequate fluid balance are all favorable factors.

Established Thrombosis without Embolism.—The foot of the bed should be elevated 4 to 6 inches and the patient allowed free movement. If cardiac or pulmonary disease seems to require elevation of the thorax, pillows may be placed under the head and shoulders, or the head of the bed may be cranked up a few inches, but flexion at the hips should be avoided and the feet should be kept higher than the face. Such treatment is especially appropriate in young and middle-aged persons in whom healing without embolism is the rule. In a week or ten days the positive dorsiflexion sign and tightness or tenderness of the calf should disappear. Then, exercise of the legs and thighs, preparatory to getting up, should be increased.

In two weeks semi-elastic bandages should be applied from toes to knee and brief periods of walking tried. After exercise, return to bed (foot still elevated) rather than sitting in a chair is desirable. If discomfort in the calf, lameness on walking, and blueness with edema of the foot and ankle remain absent, activity is steadily increased until an active life is resumed.

Failure of such treatment is indicated by a return of discomfort within the calf, by blueness and edema on dependency, or even by pulmonary embolism. Surgical treatment, to be discussed shortly, is then the procedure of choice.

Established Thrombosis with Embolism.—The chance that a fatal embolism will occur following a nonfatal infarction is perhaps one in five. The danger is sufficient to warrant an attempt to cut off the source of embolism surgically, but not great enough to condemn further conservative treatment, as just described, particularly if heparin is available. Indeed, *heparinization* may properly be combined with nonoperative treatment from the beginning. Before giving heparin, the clotting time should be ascertained by the capillary glass tube method.

Heparin* may be given by either one of two technics:

1. A 17-gauge needle having been passed into a vein of the hand or arm as for any venoclysis, 100 mg. of heparin (10,000 Toronto units) in 1000 cc. of 5 per cent glucose solution (1000 units to each 100 cc.) are allowed to run in at a rate of about 25 drops a minute. From then on, as checked by repeated study of the clotting time, heparin should be introduced in sufficient concentration to secure a clotting time of from ten to twenty-five minutes.

2. About 60 mg. of heparin (plus or minus) are introduced into the veins by individual punctures every four hours, the clotting time being checked as before. This latter method, theoretically the less accurate, is also less cumbersome and is certainly acceptable.

Heparin should be given for from three to five days and should then gradually be withdrawn over a two-day period. Occasionally, after sudden withdrawal, thrombosis recurs.

Exploration and division of a great vein to head off further embolism depend greatly upon the identification of the source of the emboli. This will usually be accomplished by physical examination (positive dorsiflexion sign, tender calf, blueness of foot on dependency). *Venography* will be of great aid in discovering the location and extent of the process. This examination, now being standardized (1941-42), requires cannulization of the lesser saphenous vein back of the external malleolus and the injection of 20 cc. of a 50 per cent compound solution of diodrast (organic iodides) at a rate of about 1 cc. per second. An x-ray plate taken immediately should give information concerning thrombosis in some of the veins in the lower leg and of any thrombus in the popliteal or femoral vein.

Thrombophlebitis (Phlegmasia Alba Dolens)

The disease attacks individuals of any age and either sex,

* There are available at least three preparations of heparin, all in the form of the sodium salt: the heparin of the Connaught Laboratories (Toronto), Lederle's Heparin, and the Roche-Organon "Liquaemin." All three liquids are supposed to contain 10 mg. of the pure crystalline salt per cc. Though the units of the Toronto product and "Liquaemin" are not the same, the actual potencies are probably very nearly identical.

occurring after childbirth as "milk-leg" and after operations and injuries which confine patients to bed. It appears rather later than phlebothrombosis and may develop from it.

Pathologic Physiology.—A variable, usually marked, inflammatory reaction with exudate surrounds the upper femoral and iliac vessels, both vein and artery. This causes, directly, local arterial constriction and, reflexly, by involving perivascular nerves, occasions diffuse peripheral vasoconstriction. The thrombus is solid, involving a variable length of the main vein and its collaterals. It mounts higher (to common iliac) on the left than on the right (common femoral). Venous obstruction, peripheral vasoconstriction and lymphatic involvement about the main vessels, in varying proportion, cause edema.

The artery is rarely thrown into intense spasm, imitating arterial embolism, causing ischemia, and even leading to gangrene of the foot. Moderate constriction is common, diminishing the peripheral pulses.

Course.—This is quite variable, ranging from ten days to many months, and tending to leave behind some edema and discomfort, with ultimate recovery except for occasional postphlebitic indurations, ulcerations and pain complexes in the lower leg. There is usually edema of the whole leg and pain in the groin and thigh, radiating behind the knee, slight cyanosis, tenderness over the femoral vessels in the groin (whether or not lymphadenitis is present) and sometimes over the iliac vessels in the pelvis. Fever ranges up to 102° F., subsiding with the active clinical signs.

TREATMENT.—Embolism is not to be feared. The foot of the bed should be elevated 4 to 8 inches and the patient encouraged to move the leg. To secure vasodilatation, no ice should be used, but body and legs should be covered with a cradle heated to about 80° F. A hot water bottle or poultice may be applied to the groin.

Lumbar Sympathetic Procaine Block.—Especially when pain or discomfort, edema and cyanosis are features of the disease, sympathetic paralysis, even though temporary, will produce an immediately favorable result which often lasts far longer than the effect of the procaine and, repeated if

necessary, rapidly and perhaps permanently does away with edema.

The procedure requires skill. For any but a light, thin man a 5-inch needle, 19 gauge with filler, is usually required; for a woman, a 4-inch needle, such as is used for lumbar puncture. One per cent procaine in any amount up to 50 cc., without epinephrine, is injected.

Two technics for this procedure are available:

1. Opposite the interspace between the first and second lumbar spinous processes and about 6 to 7 cm. lateral to the midline (a spot close to the twelfth rib and near the outer border of the erector spinae muscles) a wheal is made. Through this, the sensitive lumbar aponeurosis is infiltrated, using a fine needle.

The long needle is directed through the wheal between two transverse processes (may be touched and avoided at a depth of $1\frac{1}{2}$ to 2 inches) at an angle of about 35 degrees with the plane of the back and toward the vertebral body, *which it must strike*. It is then partly withdrawn and redirected more laterally, meeting the vertebral body at a still greater depth (usually about 4 inches from the skin in males and over 3 inches in females). Again redirected, it must glide past the vertebral body and not more than $\frac{1}{4}$ to $\frac{1}{2}$ inch deep to its last contact (danger of wounding aorta on the left side). Here it meets with the sympathetic chain, in a long up-and-down, triangular corridor formed by vertebral bodies, psoas muscle and peritoneum. Before injecting, make suction to be sure a blood vessel has not been pierced.

The injection of 10 to 50 cc. of the procaine solution (the fluid must flow in easily) through one needle will almost invariably paralyze the whole lumbar sympathetic chain, causing heating of the toes and foot, change of color to pinkness, wrinkling of the skin, and usually the appearance of distended veins of the foot (increased arterial flow to the leg).

2. Opposite the three upper lumbar interspaces and two fingers' breadths lateral to the midline (about $1\frac{1}{2}$ inches) a series of wheals is made. Through each wheal the sensitive lumbar aponeurosis is infiltrated.

Needles are then inserted successively, in a direction vertical to the plane of the back, through these wheals, to strike a transverse process. Each is then redirected, up or down, somewhat medially, and with the plan of striking the body of the vertebra

and gliding by it in each case for $\frac{1}{4}$ to $\frac{1}{2}$ inch, as in technic 1. Ten cc. of procaine is then injected through each needle.

By this technic the direction of each needle is such that its point cannot strike and injure the aorta (or vena cava). The space containing the sympathetic chain is less readily found but by using three needles, one or more will usually reach it. Considerable pain may be inflicted as the needle passes close to the large lumbar nerve roots.

Further treatment of thrombophlebitis, whether or not the sympathetic block has been used, comprises increasing exercise as the edema diminishes and the leg becomes less unwieldy. Exercise is limited to gentle movements as long as fever continues, not because of the danger of embolism, but because of the inflammatory reaction and lymphadenitis which is usually present. Lessening of local tenderness over the femoral (and iliac) vessels may be expected to accompany lysis of the fever.

Once the acute signs are relieved, exercise out of bed, in a semi-elastic bandage or stocking (toes to knee), should be taken. Between bouts of exercise the leg should be elevated. During the critical period of early use of the leg, the patient continues to sleep with the foot of the bed elevated, so that tissue fluids may drain into the body at night; in fact, the leg should never be left relaxed and dependent. Elastic pressure opposes the tendency to edema, cyanosis and dilatation of the surface veins, a tendency which slowly, after many months, diminishes.

THROMBOSIS OF THE SUPERFICIAL VEINS

Axillary Thrombosis; Effort Thrombosis

This form of thrombosis, usually a result of an unaccustomed strain in working overhead with the arm or of a fall, occurs in adult life and in either sex.

Pathology.—The axillary vein is involved probably by the tearing of a particular valve. Obstruction is the rule. There is a variable degree of peripheral extension. The veins of the arm and about the shoulder are engorged and edema of the arm and hand occurs.

Course.—The disease lasts several weeks, seldom longer, and is followed only occasionally by discomforts. Embolism is almost unknown.

TREATMENT.—Rest in bed is required. The arm should be elevated on a pillow. The re-establishment of the original or a collateral circulation is marked by subsidence of the edema and engorged veins. Exercise may gradually be resumed as edema and venous congestion subside. Sympathetic procaine block in the upper thoracic region, in cases marked by particular discomfort and edema, has been recommended. a procedure rather difficult and, as compared with lumbar sympathetic block, liable to hazard because of the danger of piercing the pleura or lung.

Thrombosis in Nonvaricose Superficial Veins

Unpredictably, thrombosis occurs in persons of either sex having normal or only locally dilated veins. Minor injuries, chafing, or exposure may excite it. In the form known as *phlebitis migrans*, it is almost exclusively confined to males, probably because of a background of fungus infection and smoking. whether or not other evidences of thrombo-angiitis obliterans (*q.v.*) are present.

Pathology.—The thrombosis is loose, soft and clotlike except in its migrating form, which is inflammatory; but embolism in either sort is rare.

Course.—The disease is obstinate, often prolonged, and recurrent unless the exciting factor is relieved. In males visible surface veins are gradually or intermittently involved. In females a quieter disease, concealed by fat, may progress with little local soreness and even propagate loosely into the femoral vein, causing embolism.

TREATMENT.—If the vein can be identified (greater or lesser saphenous), the disease is very favorably influenced by division at the groin (or popliteal space). This thrombosis actually subsides more rapidly than any other upon life in bed, the foot of which is elevated, and local application of heat. But if untreated, it tends to recur and extend.

Tobacco smoking may be so important a factor that in some instances of recurrent, migrating thrombosis withdrawal

of tobacco, without other treatment, has appeared curative. Fungus infections of the feet may affect the veins (1) possibly by an allergic effect in those who are hypersensitive, or (2) by the introduction, through the lymphatics, of secondary perivenous infection, and should therefore be eliminated if possible.

Thrombosis in Varicose Veins

Thrombosis occurs in dilated, tortuous and sacculated veins, usually just below the knee, occasionally above.

Pathology.—Overstretched endothelium and fibrosed wall of the vein explain thrombosis. Infection from the toes (secondary to fungus) may be a contributing factor. The thrombus is rather inflammatory and solid but only temporarily obstructive. A thrombosed varicose vein is eventually canalized. Embolism is very rare.

Course.—Progressive upward extension is favored by walking and standing without elastic support and by a reclining position in bed. Extension to the saphenous opening is common, whereas extension into the femoral opening is rare.

TREATMENT.—Ambulatory treatment is justified in cases with little redness and induration, particularly when the process can be covered by an adhesive, elastic bandage entirely below the knee. A hairy leg should first be shaved. The bandage is applied from toes to the crease at the knee and the patient goes about as usual. It is worn for about ten days, then removed and, if necessary, reapplied.

A process already above the knee, but which has not reached the saphenous opening, is greatly shortened by high division of the saphenous vein at the groin. Little bandaging is afterwards required.

A process which has reached the saphenous opening should be treated by rest in bed, the foot of which is elevated 4 to 6 inches. The patient should not sit up or recline. In several weeks the vein is canalized. Therefore, it had better be subjected to high division, a procedure which may even safely be performed at an early stage since detachment of a fragment of the adherent thrombus is very unlikely.

Thrombosis in a varicose vein is very slowly organized and

absorbed under a reclining position in bed and the application of ice. This treatment is mentioned to be condemned. Elevation, freedom of motion, and the application of heat are the essentials of treatment in bed if conservative methods, rather than high division, are to be used.

VARICOSE VEINS

Varicosity is incompetence of the superficial veins of the legs—because of disabled valves, overstretching and fibrosis—to forward blood against gravity toward the heart. Varicose veins are drained by communicating veins into the capacious, protected, deep system within the muscles. Varicosity is proved by a down-flow of blood (*Trendelenburg test*) when the leg is lowered. The load upon the deep system is always lessened by prevention of down-flow in, or obliteration of, varicose veins.

Even if obliteration of varicose veins in local areas at or below the knee can be secured by the injection of sclerosing solutions, stasis and back-pressure in the saphenous system at large are only temporarily interrupted. Except to aid in healing a disabling ulcer, injection should be used only as an adjunct to division ("high ligation") at the saphenous opening in the groin, a surgical procedure. The technic for local injection is described under the treatment of varicose ulcer.

Varicose Ulcer

Varicose ulcer is located in the lower third of the leg on the mesial or anterior surface, rarely below the malleoli or laterally. Usually it "rides" a vein. Stasis, ill-nutrition of the skin, trauma and infection are combined causes.

TREATMENT.—The most permanent sort of cure is secured by high division of the great (or lesser) saphenous vein plus local treatment, to be discussed shortly.

Palliative Injection Treatment.—Identify the vein to which the ulcer is tributary. Several inches above the ulcer, inject the vein by one of two technics, using a 2-cc. ampule of quinine (4 grains) and urethane (2 grains) or 2 to 4 cc. of sodium morrhuate (5 per cent).

1. After filling the syringe with the solution, insert the needle into the full vein; draw a few drops of blood and inject. Place a pad on the spot as the needle is withdrawn and attach it with adhesive and light bandage.

2. Using two syringes, insert the needle into the full vein and draw blood into the empty syringe. Detach that syringe and elevate the leg to a horizontal position, emptying the vein. Attach to the needle already inserted into the vein the syringe containing the solution, being sure that the needle is still in place, and inject. Use pad and bandage as before.

Local Treatment of the Ulcer.—In the early infected stage of free discharge and unhealthy granulations, use daily soaks of warm permanganate solution (1:3000 and stronger) which will benefit any dermatophytosis present. Apply a rubber sponge over a 10 per cent boric acid or a 50 per cent cod liver oil ointment (add 10 per cent sulfathiazole if an antiseptic is desired, but expect absorption of the drug); lay on several layers of gauze and apply firmly a semi-elastic bandage from toes to knee. Make daily dressings until the ulcer is clean and shallow. Then use a scarlet red 5 per cent or cod liver oil 50 per cent ointment, or apply adhesive strapping directly over the ulcer and neighboring leg.

High division and injection are usually useless if the communicating veins are incompetent (to find out, elevate the leg; apply constriction to thigh; lower the leg; constriction prevents back-flow, but varicose veins below the constriction fill from the deep veins). In that case, daily bandaging, elastic stocking and palliative treatment should be used, or high division plus dissection of the lower leg. Incompetency of the communicating veins is common only after thrombophlebitis.

Postphlebitic Ulcers

Postphlebitic ulcers are characterized by an erratic distribution in the lower leg. They are painful. Any veins present tend to be straight and hard and have appeared since the thrombophlebitis. Discoloration and induration are extensive. Dermatophytosis is usually present.

Treat like varicose ulcer. Excise any varicose veins present. Avoid sclerosing injections. Radical surgery may be required.

RECENT ADVANCES IN THE TREATMENT OF PNEUMONIA*

FRANCIS C. LOWELL, M.D.†

THE use of sulfadiazine in the treatment of pneumonic infections was discussed in these clinics a year ago.¹ This drug has come into general use and appears to offer definite advantages over sulfathiazole and sulfapyridine. There are no new sulfonamide drugs for the treatment of pneumonia. However, more experience has been gained in the use of the sulfonamide drugs and the management of the toxic reactions arising from them. Furthermore, a clearer concept of the incidence and clinical characteristics of viral pneumonia has developed which has decreased the confusion which so frequently arises when patients fail to respond to chemotherapy. An accurate etiological diagnosis and a careful appraisal of the patient's clinical status are essential. It is my purpose, therefore, to discuss the etiological diagnosis of pneumonia and the administration of the sulfonamide drugs and to outline the measures to be taken for the recognition and management of the toxic reactions which may arise during chemotherapy.

ETIOLOGIC DIAGNOSIS OF PNEUMONIA

Bacteriology

In every case of pneumonia a *blood* and *sputum culture* should be made before chemotherapy is begun in an attempt to make an etiological diagnosis, even though the information gained may not be available until after treatment has been started. Sputum should be obtained from the lung by encouraging the patient to cough after first having him clear

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his mouth and throat of mucus and nasal discharge. Sputum containing blood mixed through it usually comes from the lung and is almost always satisfactory for bacteriological examination. When no sputum can be obtained a *throat culture* should be made. Care should be taken to avoid letting the swab dry. If possible, it should be plunged directly into 2 to 3 cc. of a suitable culture medium and immediately sent to the laboratory. Sputum from the nasopharynx, as well as throat cultures, are much less satisfactory because such specimens usually contain a variety of organisms unrelated to the patient's disease.

An etiologic diagnosis based on the organism recovered from the blood culture, when this is positive, is reliable. Occasionally a blood culture becomes contaminated with an organism unrelated to the patient's infection. When this is suspected, several blood cultures should be obtained. The staphylococcus is one of the common contaminants in blood cultures giving rise to confusion. Pathogenic strains of staphylococci may be recognized as a rule because they produce pigment, cause hemolysis on blood agar and produce coagulase. Organisms which are not pathogenic rarely have these characteristics.

The interpretation of the findings in the sputum and throat culture may be difficult if several pathogenic organisms are present and the blood culture is negative. More than one type of pneumococcus may also be present. The etiologic diagnosis must then depend on the clinical characteristics of the infection and the relative preponderance of the various organisms present in one or more specimens.

Bacterial Pneumonia

The organisms which most frequently cause pneumonia are the pneumococcus, the hemolytic streptococcus, Staphylococcus aureus and Friedländer's bacillus. Certain pneumococcal types are especially common as causes of pneumonia. These are Types I, II, III, V, VII and VIII in adults, and Types I, VI and XIV in children. When these types are present in the sputum they are likely to be the cause of the pneumonia. This is especially true of Types I and II. The

so-called higher types of pneumococcus may often be present in the throat of normal or ill subjects without causing any evidence of infection.

The possibility of the tubercle bacillus as the cause of a pneumonia-like picture should also be kept in mind.

Viral Pneumonia

The bacteriologic diagnosis of viral pneumonia is possible only insofar as it is a diagnosis of exclusion. The diagnosis can sometimes be established when suitable measures are taken but these require special facilities and weeks or months to complete. Patients with pneumonic infection in whom no bacterial etiology can be determined may be suspected of having a viral infection, especially if the clinical picture is consistent with such a diagnosis. The clinical picture of viral pneumonia may occasionally be associated with rickettsial infection.

CLINICAL ASPECTS OF BACTERIAL AND VIRAL PNEUMONIA

The outstanding characteristics of pneumococcal and viral pneumonias are illustrated in Table 1.

Bacterial Pneumonia

Pneumococcal pneumonia frequently occurs in apparently healthy individuals. The higher types of pneumococcus often produce a less characteristic picture than the lower common types. Pneumonia caused by the hemolytic streptococcus and the staphylococcus often develops in a patient who is ill with some other disease, especially with upper respiratory or with viral infection. Pneumonia caused by Friedländer's bacillus is usually very severe, and bloody sputum is a prominent feature. The distribution of the consolidation is likely to be lobar in pneumococcal and Friedländer's bacillus infections, and is less commonly lobar in infections due to the streptococcus and staphylococcus.

In this group of bacterial pneumonias, in contrast to viral pneumonia to be discussed below, chills occur frequently, consolidation is usually outstanding, the sputum is usually

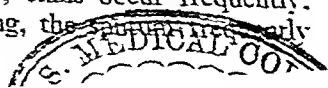


TABLE 1
COMPARISON OF THE CLINICAL FEATURES WHICH USUALLY CHARACTERIZE PNEUMOCOCCAL AND VIRAL PNEUMONIA

Etiology	Onset	Chill	Pleurisy	White Count	Blood Culture	Sputum	Chest Signs	Therapeutic Response
Pneumococcus,	Abrupt	Present	Present	16,000 to 30,000	May be positive	Bloody	Frank consolidation. Lobar	Good
Virus,	Insidious	Rare	Rare	4,000 to 14,000	Negative	Little sputum; no blood	Patchy and variable	None

contains blood, and the leukocyte count is almost always 16,000 or more. In elderly individuals, alcohol addicts, in patients with chronic disease and in certain instances of overwhelming infection a low leukocyte count may be present.

Viral Pneumonia

Pneumonia due to a virus usually lacks an abrupt onset, chills, rusty sputum and pleuritic pain. The leukocyte count is ordinarily not above 14,000 and signs of consolidation in the chest are often minimal. Chest signs may vary from day to day both with regard to intensity and location. X-ray of the chest may reveal much more lung involvement than is suspected from the physical examination. Absence of clinical response to sulfonamide therapy is also helpful in differentiating bacterial and viral pneumonia, although such information is only available at a time when bacteriologic and clinical studies of the patient have already yielded more reliable information. Failure to respond to chemotherapy alone should not be relied upon to make a diagnosis of viral pneumonia. For example, severe bacterial pneumonia may respond very slowly to chemotherapy, purulent complications may develop, or toxic manifestations of the drug may produce the picture of continued infection in the patient.

INDICATIONS FOR CHEMOTHERAPY

All patients with pneumonia should receive chemotherapy unless a contraindication exists. This is true even when, on clinical grounds, the infection appears to be caused by an organism which is unaffected by chemotherapy. Administration of one of the sulfonamides is justified under these circumstances because it is usually impossible to make a complete etiologic diagnosis at the time the patient is first seen and because there is always the possibility that the clinical impression is wrong. An accurate etiologic diagnosis is helpful in such cases in the evaluation of the course of the disease. A decision should be made after twenty-four to forty-eight hours of chemotherapy as to whether treatment is having or is likely to have a favorable effect.

In cases of pneumonia caused by virus, the tubercle bacil-

lus and probably rickettsia, chemotherapy has no apparent effect on the course of the primary infection. Patients are seen with active tuberculous infection in whom the administration of a sulfonamide drug is followed by a fall in temperature and improvement in the clinical status of the patient. Such patients very probably have in addition to the tuberculous process a pyogenic infection which is benefited by chemotherapy. In virus pneumonia in which secondary invasion of the lung with pathogenic bacteria occurs, chemotherapy is indicated. Secondary invasion may be recognized by the appearance of one or more of the following: (1) increasing numbers of pathogenic organisms in the sputum, (2) the development of a bacteremia, (3) an abrupt rise in the leukocyte count, and (4) shaking chills. *Streptococcus hemolyticus* and *Staphylococcus aureus* are common secondary invaders in preexisting virus infections.

When the infecting organism is a pneumococcus, streptococcus, staphylococcus or Friedländer's bacillus, chemotherapy is clearly indicated. In the evaluation of the clinical course of patients receiving chemotherapy, it should be remembered that infections due to the streptococcus respond less rapidly and less dramatically to chemotherapy than infections due to the pneumococcus. Staphylococcus infections also respond slowly. Experience in the treatment of Friedländer's bacillus pneumonia is limited, but even with sulfadiazine the therapeutic response is not comparable to the results obtained in pneumococcal infections.

Choice of Sulfonamide Drug

Sulfadiazine is effective against the pneumococcus, streptococcus, staphylococcus and Friedländer's bacillus and, at the present time, appears to be the drug of choice. If sulfadiazine is not available, *sulfathiazole* should be used since this drug is effective against the staphylococcus and possibly Friedländer's bacillus as well. *Sulfapyridine* has the disadvantage of causing nausea and vomiting in a high percentage of treated cases but it may be used in pneumococcal or streptococcal infections. There seems to be little place for *sulfanilamide* in the treatment of pneumonia. This drug should only

be used in the presence of infection with the hemolytic streptococcus when, for one reason or another, sulfadiazine or sulfapyridine cannot be used.

Sulfadiazine is the least toxic of the four drugs under consideration. As clinical experience accumulates, *toxic reactions* may be found to occur more frequently than is apparent at present. The reported toxic reactions to sulfadiazine include headache, nausea and vomiting, drug fever, dermatitis, leukopenia, anuria, hematuria and thrombocytopenic purpura.² A case of agranulocytosis due to sulfadiazine has also occurred in the Boston City Hospital.³ Sulfathiazole causes drug fever, rashes and hematuria relatively frequently and there are reports of anuria, acute hemolytic anemia and agranulocytosis following its use. These toxic reactions have also followed the use of sulfapyridine. Except for renal manifestations of toxicity, this is also true of sulfanilamide.

ADMINISTRATION OF THE SULFONAMIDE DRUGS

In individuals of various size and age, estimation of the daily dose may be made on the basis of weight. Opinion differs with the regard to the administration of alkali except when sulfanilamide is used, in which case 1 gm. of sodium bicarbonate should be given with each gram of the drug. Because the rate of absorption of the sulfonamide drugs from the gastro-intestinal tract and the rate of excretion by the kidneys may vary widely, blood levels in the individual patient cannot be predicted on the basis of dosage. For this reason, daily determination of the concentration of the drug in the blood may be necessary.

Administration of Fluids

The excretion of the sulfonamide drugs is almost entirely by way of the kidneys. A large urinary output is an important safeguard against the development of renal complications which are apparently more likely to follow when high concentrations of these drugs are present in the kidney and urinary tract. Therefore, patients should receive 3000 cc. of fluids in twenty-four hours or a sufficient amount to insure a

urinary output of 1500 cc. in twenty-four hours. Recording of the fluid intake and output is important.

Drug Levels in the Blood

The only reliable method for gauging the dose of the sulfonamide drugs accurately is to make repeated blood level determinations. When the drug is administered parenterally, blood should be taken at the end of an interval between doses. It is just as important to determine whether the concentration of the drug in the blood is dangerously high, as a result of failure to excrete the drug at the usual rate, as it is to know whether the concentration is high enough to be therapeutically effective (see Table 2). In the less severe

TABLE 2
EFFECTIVE RANGE OF THE CONCENTRATION OF THE
SULFONAMIDE DRUGS IN THE BLOOD

Drug	Concentration in Mg. per 100 cc.	
	Effective	Maximum
Sulfanilamide.	6-10	15
Sulfapyridine	4-7	12
Sulfathiazole	2-6	10
Sulfadiazine	6-12	20

cases the response to chemotherapy is often rapid, and the determination of the blood levels may frequently be dispensed with after the first twenty-four hours of treatment.

In Table 2 are shown the average therapeutic levels of the four sulfonamide drugs used in the treatment of pneumonic infections, as well as the maximum levels which may be considered safe. For general purposes, determination of the free or uncombined drug in the blood suffices. If patients are treated for a week or more, or if signs of renal failure develop, it is advisable to have determinations made for the acetylated or combined drug as well. Determinations of the

acetylated drug are especially important when sulfapyridine and sulfanilamide are used as these drugs are acetylated in the body in comparatively large amounts.

Routes of Administration

ORAL ROUTE.—This is the route of choice and should be used unless: (1) nausea and vomiting are sufficiently severe to make oral medication impractical; (2) the patient is unable to swallow; (3) satisfactory blood levels cannot be obtained. The dosage of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine is about the same, namely: 6 to 8 gm. in twenty-four hours for patients weighing 60 to 80 kg. An initial dose of 4 gm. followed by 1 gm. every four hours will usually give a concentration of the drug in the blood which will lie within the therapeutic range. The pills may be crushed and mixed with food or fruit juices. In patients who are irrational or are in coma the sulfonamide drugs may be administered by stomach tube, in which case the pills must be finely ground in order to avoid obstructing the tube.

RECTAL ROUTE.—Sulfanilamide is the only one of the four drugs under consideration that is absorbed from the rectum in therapeutic amounts.

PARENTERAL ROUTE.—As sulfadiazine, sulfathiazole and sulfapyridine are very insoluble, the sodium salts of these drugs dissolved in saline or distilled water must be used for parenteral administration. The drugs may be given intravenously or subcutaneously. The sodium salts of the sulfonamides form highly alkaline solutions and they are irritating to the tissues when concentrations of more than 1 per cent are used.

The *intravenous* route is most valuable when rapid saturation of the patient with a sulfonamide drug is desired. Further administration is best made by the oral or the subcutaneous routes. An initial intravenous dose of 5 gm. may be conveniently given from a large syringe in a volume of 100 cc., making a concentration of 5 per cent. This solution should not be introduced into the perivenous tissues. Such a dose administered over a period of about ten minutes will give a concentration in the blood between 10 and 15 mg. per 100 cc. The blood level will fall quickly thereafter. Further doses

of 2 to 3 gm. every six to eight hours may be given over a period of forty-five minutes to one and one-half hours in a concentration of 0.5 to 1 per cent. However, the subcutaneous route is preferable for this purpose.

The *subcutaneous* administration of the sulfonamide drugs is indicated when continued parenteral chemotherapy is necessary. The sodium salts of the sulfonamide drugs should be administered subcutaneously in concentrations not greater than 0.8 per cent. An initial dose of 5 gm. in 700 cc. of saline or distilled water may be injected over a period of forty-five minutes to one and one-half hours and further doses of 2 to 3 gm. may be given at eight- to twelve-hour intervals. Intradermal injection of novocain at the site of entry of the clysis needles contributes to the comfort of the patient, but the addition of novocain directly to the solution of sulfonamide drug is contraindicated on theoretical grounds because novocain acts like para-aminobenzoic acid in inhibiting the bacteriostatic and bactericidal action of the sulfonamide drugs.

Adjustment of Dose; Indications for Withdrawal

When the sulfonamide concentration in the blood is too low the dose may be increased to 1.5 or 2 gm. every four hours for three or four doses. If this fails, parenteral administration may be used. The fluid intake should not be decreased for this purpose except in the case of sulfanilamide. When the blood level is too high the administration of the drug should be decreased or stopped temporarily. High levels often result from diminished excretion of the drug by the kidneys. This may occur because of insufficient fluid intake or because of renal damage. When an unexpectedly high level is discovered a nonprotein nitrogen determination should be obtained and the possibility of the presence of severe hematuria, oliguria or anuria should be carefully investigated.

Indications for Stopping Chemotherapy:

1. A normal temperature and pulse for a period of forty-eight hours or more. It is probably advisable to continue chemotherapy until at least seven days have elapsed since the onset of the pneumonia.

2. The development of certain toxic manifestations of sulfonamide therapy (see Contraindications below).

3. The absence of therapeutic response within forty-eight to seventy-two hours after chemotherapy was started, on condition that no specific indication for continued chemotherapy exists.

Contraindications

Sulfonamide therapy is contraindicated in patients who give a history of having had or who develop (1) acute hemolytic anemia, (2) severe oliguria or anuria, or (3) agranulocytosis, as a result of treatment with the sulfonamide drugs. It is usually safe to continue chemotherapy in the presence of nausea and vomiting, microscopic hematuria and a slowly progressive anemia. When fever or rash develop during chemotherapy, treatment should be stopped or one of the other sulfonamides should be tried. In certain instances of severe infection it may be less dangerous to the patient to continue therapy with the same sulfonamide drug in the presence of a mild rash or hematuria of moderate degree if the drug being used is the most effective for the treatment of the patient's infection.

TOXIC MANIFESTATIONS OF THE SULFONAMIDE DRUGS

The toxic reactions which accompany treatment with the sulfonamide drugs give rise to difficult diagnostic and therapeutic problems. The time required for the development of the various toxic reactions⁴ is shown in Table 3, which also contains suggestions for treatment. In individuals who have received one of the sulfonamide drugs on a previous occasion, the incidence of reactions is higher and the reactions may develop much more rapidly than is indicated in the table. Fever may appear within a few hours of the initial dose and a rash may develop within a day or two. The incidence of fever following the readministration of sulfathiazole was recently studied under controlled conditions and was found to occur in 36 per cent of patients.⁵

TABLE 3
TOXIC REACTIONS TO THE SULFONAMIDE DRUGS

Reaction	Usual Time of Onset after Starting Chemotherapy*	Treatment	Remarks
Rash	5 days or more	Stop chemotherapy or change to another sulfonamide drug if further treatment is indicated.	Usually morbilliform. Rarely itchy. Sulfathiazole may cause lesions like erythema nodosum.
Fever	3 to 7 days	Stop chemotherapy or change to another sulfonamide drug if further treatment is indicated.	Temperature falls in a few hours when drug is stopped.
Acute hemolytic anemia	2 to 6 days	Further sulfonamide therapy contraindicated. Transfuse. If severe, give sodium bicarbonate until urine pH is 7.0 or above.	May develop very rapidly.
Slowly progressive anemia	1 week or more	Transfuse to maintain hemoglobin. Stop chemotherapy or change to another drug if severe.	
Leukopenia	2 weeks or more	Do daily leukocyte counts and smears.	
Agranulocytosis	2 weeks or more	Further sulfonamide therapy contraindicated. Give pentothal and transfusions.	Not dangerous in itself. May be precursor of agranulocytosis.
Microscopic hematuria	Within first 10 days	Insure urinary output of 1500 cc. or over. Chemotherapy may be continued.	Highly fatal.
Gross hematuria	Within first 10 days	Stop chemotherapy. When urine returns to normal, sulfathiazole or sulfanilamide may be given.	May give rise to renal colic.
Oliguria and anuria	Within first 10 days	Further sulfonamide therapy contraindicated. Insure fluid intake of 3000 cc.	May be fatal.
Jaundice	2 to 6 days	Usually hemolytic type due to acute hemolytic anemia mentioned above—treatment is the same.	
	2 weeks or more	Stop chemotherapy or change to another drug.	Probably due to sensitization to drug.

* Patients who have received a sulfonamide drug on a previous occasion may develop toxic reactions very quickly when given a second course.

TABLE 4
PLAN OF LABORATORY PROCEDURES IN PATIENTS RECEIVING CHEMOTHERAPY*

	Day of Treatment						
	Second	Third	Fourth	Fifth	Sixth	Seventh	
<i>Blood culture</i>	Blood culture	Daily blood cultures if indicated					
<i>Sputum culture</i>	Sputum culture						
<i>Urine</i>	<i>Urine</i>	<i>Urine</i>	<i>Urine</i>	<i>Urine</i>	<i>Urine</i>	<i>Urine</i>	
Hemoglobin and red cell count		Hemoglobin and red cell count		Hemoglobin and red cell count		Hemoglobin and red cell count	
White cell count and smear		White cell count and smear		White cell count and smear		White cell count and smear	
Nonprotein nitrogen			Nonprotein nitrogen		Nonprotein nitrogen		
	Drug level		Drug level		Drug level		

* Procedures which are particularly important are italicized.

Laboratory Studies

The sulfonamide drugs cause toxic reactions with sufficient frequency to warrant careful study to aid in the recognition of such reactions as early as possible. Some of the toxic reactions may be recognized by suitable laboratory measures. Data obtained *before* the patient receives treatment is very helpful in the evaluation of abnormal findings during the course of the disease. Table 4 illustrates what may be considered a complete laboratory study in a patient receiving chemotherapy for seven days. Procedures which are particularly important are italicized. In patients who are very ill and in all patients over forty years of age, a nonprotein nitrogen determination should be made at the time treatment is begun.

SERUM TREATMENT

Serum of proved value in the treatment of pneumonia is available only for pneumococcal infections.

Indications

1. Antipneumococcus serum is indicated in all patients with pneumococcal pneumonia in whom treatment with the sulfonamide drugs is contraindicated.

2. Combined sulfonamide and serum therapy should be given to patients with pneumococcal pneumonia who fail to show improvement within twenty-four to thirty-six hours after chemotherapy is started and who, in addition, have an unfavorable prognosis as indicated by the presence of one or more of the following features: (a) positive blood culture; (b) over the age of forty years; (c) treatment started later than the third day; or (d) two or more lobes involved.

Dosage

Patients receiving serum alone should be treated as early as possible. An initial dose of 100,000 units usually suffices for the less severe cases. Further doses of 50,000 to 100,000 units should be given if improvement fails to take place within eight to twelve hours. The initial dose of serum should be doubled if the patient presents any of the four features men-

tioned above which indicate a less favorable prognosis and in patients who are pregnant.

Patients receiving combined sulfonamide and serum treatment require less serum than patients receiving serum alone. An initial dose of 50,000 to 75,000 units usually suffices. Additional doses of 50,000 units may be given if no improvement takes place within eight to twelve hours. In certain patients who are extremely ill, it may be dangerous to administer serum intravenously because of the possibility of serious consequences following even a mild reaction to the serum. In such cases 100,000 to 300,000 units may be given *intramuscularly*. The danger of vasomotor collapse or chill reactions when serum is given in this way is much less. Allergic reactions, however, cannot be avoided by this means. There is evidence indicating that the intramuscular administration of serum is wasteful of antibody and for this reason the intravenous route should be used whenever possible.

Precautions

In patients who have received injections of serum on a previous occasion or who have hay fever or asthma, serum is contraindicated or should only be given with great caution. A family history of allergy also warrants caution. Conjunctival and skin tests with diluted normal serum should always be carried out. Adrenalin should be on hand during the performance of the skin tests as well as during the administration of the serum. In the event of an allergic reaction 0.3 to 0.5 cc. of adrenalin (1:1000) should be injected subcutaneously and this may be repeated at ten-minute intervals as often as necessary.

Reactions Following Injections of Serum

Most of the immediate reactions which follow the intravenous administration of serum fall into three distinct types—*anaphylactic, circulatory and thermal*.⁶ Their differential diagnosis and treatment are given in Table 5. Serum sickness, which is also included in the table, is important chiefly because the associated fever may be confused with a purulent complication of the infection or with drug fever.

TABLE 5
REACTIONS WHICH MAY FOLLOW INTRAVENOUS INJECTION OF HORSE ANTIPNEUMOCOCCUS SERUM

Type of Reaction	Time at Which Reaction Occurs	Symptoms	Predisposing Factors	Treatment	Remarks
Anaphylactic or allergic	During or immediately after injection.	Urticaria and asthma. Collapse if severe.	Allergy. Previous injections of serum.	Adrenalin. Stop serum treatment.	May be fatal.
Circulatory	Usually immediate.	Fall in blood pressure. Collapse.	Scrum lot. Cardiovascular disease.	Adrenalin. Change to another lot of serum.	May be fatal.
Thermal	Thirty to 90 minutes after injection.	Chill and rise in temperature.	Scrum lot.	Blankets and heaters. If severe, give morphine gr. $\frac{1}{4}$. Sponge with cool water if temperature reaches 105° F. Change to another lot of serum.	Rarely fatal.
Serum sickness	Five to 12 days after serum treatment.	Lymphadenopathy, fever, urticaria and malaise.	Administration of large amounts of serum.	None.	Never fatal.

SUMMARY

The failure of certain patients with pneumonia to improve following treatment with the sulfonamide drugs may frequently be explained by one of the following: (1) the infection may be of a type which is not affected by chemotherapy; (2) the infection may be of sufficient severity to delay recovery or a purulent complication may develop; (3) the patient may develop a toxic reaction to the sulfonamide drug. The interests of the patient are served best when steps are taken to establish the etiology of the infection and the clinical status of the patient before chemotherapy is started.

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THE TREATMENT OF THE ASTHMATIC ATTACK*

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WHEN one is called to see a new patient with supposed asthma, a working conception of the pathologic nature of the process and of its probable cause should be made at once.

CLINICAL DIAGNOSIS

Does the patient have asthma, and what kind of asthma is it? Asthma is a symptom, not a disease entity. If the patient has an obstruction to the flow of air in and out of the chest, so that he makes a wheezy noise with his breathing, he has "asthma." Any obstruction, mechanical or pathologic, to the free flow of air in and out of the lungs will cause a wheeze. Constriction of the trachea or of the major bronchi will produce a very special and characteristic type, which results from the "high" obstruction. Laryngeal stridor is an obvious sign, but a foreign body at the bifurcation of the trachea will also produce a wheeze of a rather typical "high" sort. Cancer of the trachea may be suspected and almost diagnosed by the nature of the wheeze. Gumma involving the larynx and upper trachea with wheezing has been observed, and pressure on the larger air tubes from aneurysm or tumors may produce somewhat similar pictures.

In these instances in which the obstruction is in the upper part of the bronchial tree, the breath sounds to be heard over the lungs are not always abnormal. The breathing may be of normal quality and of normal intensity. In spite of the narrowing above, the air "gets in" below quite well, though coarse, dry rales produced in the obstructed area may be detected in all parts of the chest. On the ward at present is an

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elderly lady with symptoms of a high obstruction. She has a peculiarly high-pitched wheeze intensified by even slight exertion which also produces severe dyspnea. Her chest x-ray, however, shows the lungs perfectly clear, with the diaphragm at the normal level. The breath sounds are of normal character, and with no rales at all. Bronchoscopy has shown a cancer in the tracheal wall about 2 inches below the larynx. The patient wheezes and therefore she has "asthma," but her type of asthma does not yield to ordinary treatment. She does not have bronchospasm, and epinephrine does her no good.

Chronic emphysema has its onset in middle age and is usually secondary to recurrent attacks of bronchitis, but it may be "primary" and develop without obvious cause. Acute emphysema occurs with every attack of asthma when the alveoli are distended by a process which makes inspiration easier than expiration, but this process is reversible and the stretching of the alveoli subsides when the attack passes. Chronic emphysema, however, persists; the alveoli have ruptured into one another to make large empty air spaces and have thus reduced the efficiency of the lungs. The chest itself becomes distended—"barrel shaped"; the pulmonary "dead space" is much increased. The "tidal air" is restricted to the upper limit of chest expansion and does not reach the mid-position where there is room for an extra "deep breath." In emphysema the vital capacity is markedly reduced.

Clubbed fingers and cyanosis of lips, tongue and fingers accompany emphysema but are caused by the pulmonary defect which makes the aeration of the pulmonary blood mass irregular and uneven. There is a mixture of aerated and non-aerated blood in the return to the left heart. Most patients with chronic emphysema wheeze because a certain degree of chronic bronchitis producing exudate in the tube lumen is always present.

Heart disease causes paroxysmal dyspnea often but a wheeze only rarely and the mechanism of this wheeze is not clear. One can postulate that the pulmonary congestion with the marked increase in the pulmonary vascular bed which Peabody¹ demonstrated might impinge upon the smaller air tubes to narrow their lumen and so cause a wheeze, but the

idea is hard to prove. In pulmonary fibrosis, the smaller bronchi are narrowed and in pulmonary arteriolar sclerosis (Ayerza's disease) there is vascular congestion.

In the ordinary sense, however, "asthma" is a wheezy breathing which depends upon spasm of the smaller air tubes or on edema of the walls of both smaller and larger bronchi, or on both spasm and edema together. When spasm alone is present, the breath sounds are markedly diminished—"little air gets in"—and small, fine dry rales are heard evenly spread throughout the chest. When bronchial exudate appears, the signs change, moist bubbly rales appear and may have an irregular distribution. More important, the distribution of the breath sounds may be irregular. With pure spasm the diffuse lesion gives uniform signs which are evenly and diffusely heard, but with exudate, which is lodged more in one place than another and is more tenacious in one place than another, the signs vary in different parts of the chest. "Good air," as shown by a rather loud inspiratory sound in one area, may be in contrast to very little air with greatly diminished breath sounds in another area. Rales vary also; they may be small and fine in one place and coarse and noisy in another. The signs may change rather rapidly, as the exudate loosens here or becomes more tenacious and more obstructive there.

This attention to the principles of pathology and physiology is necessary before treatment can be discussed. Drugs have certain actions and should be prescribed only when that action is desirable or possible.

ETIOLOGY

What is the probable cause of the asthma? Is it allergy? Is it reasonable to consider that the cause of trouble depends upon a sensitivity to a certain dust in the environment from which the patient might escape by moving away? Or is it due perhaps to a food or a drug to which the patient is sensitive? It is the history of the illness which is most important here and it should be easy to find out on the one hand whether the asthma has occurred in rather isolated attacks related to changes in season or environment (the cause is

outside the patient's body; *i.e.*, "extrinsic"), or on the other hand whether the process has been chronic and persistent from the start (the cause is something which the patient carries with him; *i.e.*, "intrinsic"). In some cases the distinction is not too easy. Anxiety and apprehension or other "nervous factors" may complicate the picture or both extrinsic and intrinsic factors may play a role. Thus the patient may have allergy and heart disease together, or allergy with irreversible chronic emphysema at the same time. Perhaps the most helpful point is the age of onset. When asthma begins before the age of thirty years the chances that allergy is the cause are good, but when asthma begins after the age of forty-five years the chances of allergy are small and in such patients the asthma is usually intrinsic.

TREATMENT OF THE ASTHMATIC ATTACK

Home Treatment

Let us first assume that a patient has asthma which is due to spasm and edema of the bronchial mucosa, with exudate in the large as well as the small tubes. A danger is present that this exudate may become inspissated into tough sticky plugs and actually occlude one or all of the bronchi. The patient is sick and in trouble. If he is at home and the asthma is not too severe, it may be well to leave him at home. If the history reveals evidence of allergy as a reasonable explanation, one should study the environment closely. To get rid of the dog and cat, to change the mattress and pillow, or even to move the patient into the next room—such simple measures may accomplish wonders. The administration of epinephrine (adrenalin) (0.4 cc. [6 minims] of the 1:1000 solution, hypodermically) is indicated, and if the first dose relieves promptly it may be wise to teach the patient or a member of his family to inject other small doses (0.4 cc. [6 minims]) as they may be needed. The dose will be discussed presently.

Hospital Treatment

If the asthma is severe, then the patient had best be moved to the hospital. Such a move is in itself an important step in the treatment. It eliminates all domestic dusts in one maneu-

ver; it brings the patient to a new atmosphere of peace and quiet; it enables the doctor to see him easily and often; it provides a nurse to give adrenalin without difficulty or delay; and it restores his confidence. A great fault in the management of asthmatic cases is not to recognize the full importance of hospital care. The patient arrives exhausted and perhaps gasping for breath, but suddenly finds himself in a small quiet room. Why not leave him there for a few minutes to see what the change alone will do?

Epinephrine.—If the asthmatic attack is not too severe epinephrine can be given again. It is well at this point to emphasize several important details about the use of epinephrine. Epinephrine is "adrenergic"; its action is to stimulate the sympathetic system to make it overcome the effects of those "cholinergic" substances which cause spasm of smooth muscles and stimulation of glands. If bronchospasm is present, epinephrine should bring relief.

The first dose of epinephrine is often much too large. The dose is not 1 cc. of the 1:1000 solution. Epinephrine is a powerful drug and such a quantity often causes a severe reaction with pallor, trembling, palpitation and sometimes nausea. In the presence of arteriosclerosis, adrenalin can constrict the coronary vessels and produce angina. On the other hand, the small dose which is quite enough to relieve bronchospasm will thereby relieve the burden on the heart and do great good even if coronary sclerosis is present in some degree. A dose of 0.5 cc. (8 minims) is almost always effective and most patients are relieved by as little as 0.4 cc. (6 minims) or even 0.3 cc. (5 minims).

Epinephrine should bring relief within fifteen minutes. If the first small dose is not effective and does not produce any untoward sympathetic effects, such as trembling, pallor and palpitation, then another small dose can be given fifteen minutes later. Such pairs of doses, however, should not be administered more often than two hours apart. The stimulus to the sympathetic system is powerful. When the system is already stimulated to excess and like the tired horse is incapable of responding any more, further stimulation does harm.

Aminophylline.—Aminophylline is the trade name for theo-

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phylline with ethylenediamine. It is related to diuretin, a diuretic drug. The action of aminophylline in asthma is not clear but it is said to stimulate both heart and kidneys and to increase capillary permeability. It is often quite effective and can be given in various ways. The most effective method is to inject intravenously the contents of an ampule which contains grains $3\frac{3}{4}$ dissolved in 10 cc. of water. The injection should be made slowly and usually brings results within fifteen or twenty minutes. Aminophylline by mouth is not so useful but can be tried.

Dextrose and Normal Saline Infusion in Severe Cases.—Occasionally one sees a patient with severe asthma who has not responded to epinephrine administered hourly before his admission to the hospital. Aminophylline also has been injected at least once, without effect. Such a patient is in real distress. He is pale and sweaty. His pulse is rapid. He cannot lie down. Rest is out of the question. He can neither eat nor drink, his bowels have not moved and urine is scanty. His tongue and mouth will be found to be dry. He needs water and there is reason to think that he needs salt and sugar also. In such a case, the best treatment is to inject intravenously by slow drip a large amount (1500 cc.) of 5 per cent dextrose in normal saline solution. In almost all cases this treatment is successful; sometimes the infusion can be continued until a total of 3000 cc. or even more has been injected.

Just how this infusion acts is not entirely clear. Blood studies of such patients before treatment show high figures for sugar, salt and protein, evidently because the blood is concentrated. After the treatment, sugar may appear in the urine and it may be that normal saline solution without the sugar would be quite as effective as with it. After the infusion most patients are greatly relieved; the pulse slows and the color returns. The worst of the attack passes and the asthma is under a certain degree of control.

Morphine and Other Depressant Drugs Are Contraindicated.—In severe attacks of the nature just described, in which epinephrine and aminophylline have proved ineffective, no additional drugs are given. This is important. Our watchword has been "Treat them gently." We try not to get too excited

or be in too much of a hurry to stop all wheezing at once. In a quiet room with a nurse to render service and confidence the patient is reassured from the start. All drugs are withheld.

Morphine should never be used in asthma. The temptation, indeed the urge, to give morphine is very strong. Fatigue has advanced to exhaustion, apprehension and anxiety are marked, there is suffering and there is coughing often with pain in the chest. The utter misery positively begs for morphine.

In the Massachusetts General Hospital fifty patients have died in attacks of asthma and have come to autopsy. These fifty included twenty patients whose asthma began after the age of forty-five years, and each of them came to the hospital in extremis. In five instances death occurred within a few hours after admission and in each of these five morphine was given. This was before we knew the danger of morphine in asthma.

As Vaughan² has written recently, there are two principal objections to the use of morphine in asthma. (1) Morphine depresses the nervous system in general and the respiratory center in particular. Vaughan describes the case of a young girl nineteen years of age whose asthma was extreme. After morphine, her respiration fell to four a minute and she died soon. The patient cannot afford to have his respiratory effort compromised by morphine. (2) Morphine is a "cholinergic" drug. It stimulates the parasympathetic nervous system and it actually causes bronchospasm. In asthma, therefore, morphine tends to make the bronchospasm worse instead of better. Incidentally, if a drop of morphine solution is scratched into the skin of a normal person, a positive wheal and erythema reaction will result, in the same way that histamine will give an immediate skin reaction.

One patient, a woman in her late forties, was to have a bronchoscopic aspiration of tough, sticky bronchial plugs. She was given both morphine and phenobarbital as preparation—to make the operation as painless and comfortable as possible. It was!—but she almost died afterwards and was resuscitated only with great difficulty by using intravenous fluid and oxygen tents. She stayed in the hospital five weeks. A year later this same lady was subjected to bronchoscopy

again and this time the preoperative treatment consisted of a drink of cold water! The bronchoscopy was not quite so easy or comfortable but on return to the ward her condition was excellent; and she stayed in the hospital five days in place of five weeks.

What is said about morphine applies also to related substances, particularly to *codeine* and *pantopon*. These drugs should be forbidden in the treatment of asthma.

The *barbiturates* are not quite so dangerous although they too depress the central nervous system. They are objectionable because the patient may be sensitive to barbiturates just as he is often sensitive to aspirin. In one patient chronic asthma which persisted in spite of all treatments was found later to depend chiefly upon the small dose of phenobarbital which the patient took at bedtime.

Aspirin-sensitive Patients.—Aspirin has such a characteristic effect in asthma as to suggest the designation of a special group of "aspirin-sensitive" patients. These patients all have severe asthma and in most of them a dose of aspirin has at one time or another produced an almost fatal attack. One of our patients who subsequently died was extremely sensitive to aspirin. One afternoon he complained of a headache and the young nurse tried to relieve him with 5 grains of aspirin. Within fifteen minutes the man was in such respiratory distress that we thought he would die. An intravenous infusion of 5 per cent dextrose in normal saline solution, as described previously, was started immediately and in a few minutes the worst was over. The experience was terrifying, and it all depended upon a specific sensitivity to a drug which is harmless to thousands of individuals.

Drugs Permissible for Sedation.—If all these drugs are forbidden, what can be used for sedation? The fact is that if the asthma itself can be relieved, sedation becomes unimportant; the patient is exhausted and is only too ready to rest, and often will fall asleep without any extra help. Sometimes, however, apprehension and anxiety continue to such an extent as to demand treatment and in a few cases drugs with simple chemical formulas are allowed. *Chloral hydrate* is trichloroacetaldehyde in which the carbon atom has two hydroxyl

groups ($\text{CCl}_3\text{CH}(\text{OH})_2$). It is very useful, and in many patients careful regulation of the dose of chloral hydrate from the small quantity of 10 grains to the larger amount of 30 grains will change the patient from comfortable drowsiness to almost stupor. Then the small dose can be given as often as every six hours if necessary. *Paraldehyde* is a polymer of acetaldehyde (CH_3CHO)₃. It is a volatile liquid which is absorbed with great rapidity when given by mouth and less rapidly when given by rectum. The dose is 4 cc., one teaspoonful, but 8 cc., 2 teaspoonfuls, can sometimes be used. The soporific effect comes on immediately and within five or six minutes the patient will suddenly relax. One has to be careful, however, to remember that whereas such a powerful drug depresses the central nervous system as a whole, it depresses the respiratory center incidentally and so if the asthma is very severe, paraldehyde must be used with caution. For a quick effect, however, it is a useful drug.

SUMMARY

The important feature in the treatment of the asthmatic attack is to *know what not to do*. We "treat them gently" as said. We recognize that the hospital itself with its doctors, its nurses, its facilities and its services are important factors and we allow a little time for these factors to operate. We use adrenalin freely but do not expect adrenalin to accomplish the impossible. Water is important and we like to stress the need for large amounts of it. The addition of salt and of sugar appears to be helpful but whether these are necessary is not yet clear.

When the acute attack has subsided and the patient can breathe more easily, then the search for the cause of asthma and the problem of preventing further attacks can begin.

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THE TREATMENT OF SINUSITIS*

FRANCIS L. WEILLE, M.D.†

OBJECTIVES IN TREATMENT

THE objectives in the treatment of sinusitis are: (1) to obtain a cure if this is possible, (2) to obtain relief, quiescence or regression, (3) to prevent recurrences, and (4) to prevent waste of the patient's time and economic resources. The procedures in each of these objectives are discussed under the appropriate headings.

1. Obtaining a Cure

Whether a cure can be obtained depends upon the type of sinusitis with which one is dealing and upon the location of the involvement. Sinusitis may be classified as acute, subacute or chronic, and any or several of the nasal sinuses may be involved.

The *criteria for a cure* should be (1) a satisfied patient and (2) nasal and sinus physical findings of adequate excellence, backed by equally satisfactory sinus x-rays.

Acute Sinusitis.—Patients with acute sinusitis whose sinuses were normal before the attack started usually recover completely with medical treatment, and a considerable percentage have a strong tendency to get well even without treatment. While recognizing that such patients tend to do well, it is felt that they should not be allowed to develop chronically thickened membrane in the sinuses, nor should they be permitted to develop serious complications such as orbital cellulitis or abscess, through neglect of certain simple and conservative methods of management.

Subacute Sinusitis.—Patients with subacute sinusitis tend to

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its equivalent carrying about 2500 ma. of current for ten seconds or slightly less.

Even if the sinusitis in this type of patient is completely eradicated, it is very likely that no improvement will occur in the patient's nasal complaints. In other words, while many rhinologists expect improvement in the nasal mucosa to occur secondarily when infectious sinus disease is eradicated, such favorable changes do not occur in patients having vasomotor rhinitis when allergic sinusitis is so treated. An interesting observation has been that vasomotor rhinitis, complicated by an infectious cellulitis, tends to persist severely, while the infectious element tends to subside very slowly. If gramicidin comes into clinical use in the future, it is likely to prove especially valuable in helping to allay infection from gram-positive organisms complicating vasomotor rhinitis.

Acute exacerbations of chronic sinusitis may terminate in permanently aggravating the chronic condition. Effort should be made to avoid this unhappy result, as well as potentially serious complications.

Curability in Terms of Location.—It is generally agreed that the most favorable results from treatment are obtained in the antrum, the least favorable in the frontal sinus. The ethmoid and sphenoid are intermediate between these extremes.

2. Obtaining Relief, Quiescence or Regression

Relief is normally the patient's sole demand; he frequently disappears from the rhinologist's practice as soon as comfort and minimal annoyance from the disease have been attained. If the doctor anticipates that cure is not possible, he should endeavor to secure a maximum degree of regression of the sinusitis.

3. Prevention of Recurrences

A common question which the patient with an attack of acute sinusitis asks the doctor is, "If this is cured, will it come back again with the next cold?" The answer is that it may recur with any acute upper respiratory infection or with infection from swimming. The possibility of recurrence

recover under conservative methods of treatment as late as three months from the initial infection, and probably even later. Such cases should not be allowed to become chronic.

Chronic Purulent Sinusitis.—Chronic purulent sinusitis is sometimes curable by a combination of medical and surgical methods; the difficulty of cure has led to the Cahill dictum, "Once a sinus, always a sinus." In spite of such pessimism, many of these cases recover with adequate drainage. Mosher¹ has stated that 85 per cent of patients with chronic purulent maxillary sinusitis can become completely well.

Chronic Polypoid Sinusitis.—Chronic polypoid or polypoid and purulent sinusitis is interrelated in many cases with problems of allergy. The *allergist* may, but usually does not, aid materially in curing such cases, although he may help them toward relief. The *rhinologist* by his methods usually does not cure associated manifestations of allergy such as asthma. He may help to relieve asthma in about half of the so-called intrinsic cases. Of those relieved, about one in five will be apparently cured; but after several years there is recurrence so that the "cure" can only be considered a remission. The author's experience is that satisfactory improvement (for cure is rare) in the nose can be obtained in about 75 per cent of these patients, so long as the patient, the allergist, and the rhinologist work in cooperation. The nasal disease will probably never be permanently cured until the fundamental nature of allergy is better understood. This statement is made with the belief that allergic sinusitis is merely a part of the picture of allergy; not a cause, not a result, but an integrated manifestation of it.

In patients having *vasomotor rhinitis with associated sinusitis* (usually ethmoiditis with decalcification of cell partitions) it is likely that the greatest progress can be made by efforts directed toward improving the nasal cavities themselves. This means the correction of mechanical defects in the nose, such as a deviated septum or hypertrophied anterior tips of middle turbinates, at the same time making an effort to stabilize the unstable nasal mucosa. The best method for accomplishing the latter is conservative linear subepithelial *diathermy coagulation* of the inferior turbinates with a Keith needle or

sinusitis and nasal polyps, that polyps and polypoid tissues tend to recur when exenterated, not only from the nasal cavities but from the sinuses as well. An effort must be made more or less indefinitely to control this tendency—for example, by *diathermy coagulation* of such tissue as it starts to grow.

4. *Never damage the function of normal nasal structures.* Preserve ciliary activity in the sinuses and nasal cavities so that the normal self-cleansing physiology may be retained. Do not destroy or injure the air-conditioning function of the nose in warming and moistening inspired air preparatory to pulmonary ventilation. Proetz² estimates that about 680 cc. of water and 2.5 per cent of body heat are required daily for these functions. Moreover, this same author's theory that the sinuses serve as insulation for the nasal cavities is attractive and exercises a restraining influence upon overenthusiastic surgical technics.

5. *Endeavor to relieve swelling of the nasal mucosa in the region of sinus ostia.* In a very high percentage of cases, the relief of such swelling will allow drainage to occur by ciliary activity; i.e., the self-cleansing physiological mechanism of the nose and sinuses must be allowed to function as far as possible in any type of sinus disease. Remember that an ostium may be anatomically a tunnel, i.e., it may have length as well as being a simple window.

6. So long as pus from a sinus *drains well* in acute or sub-acute sinusitis, do not be disturbed by the presence of further secretion in the sinus. For example, the mere presence of pus in the antrum is no justification for "washing" the antrum, any more than the presence of pus in a boil on the neck is an excuse for irrigating the boil. It is establishing drainage that is important, since pus not under pressure does little harm. The writer gave up antral washing years ago (except in rare instances through the middle meatus with extreme gentleness).

7. *Infection alone does not interfere with ciliary function.*²

8. *Strong suction must never be applied to the nasal cavities as a whole.* On the contrary, weak "spot" suction is employed. This means about 3 or 4 pounds of negative pressure,

should not be a justification for poor management. Certain precautions can be exercised to limit the probability of such further attacks. Two of the best such measures are to make certain, if possible, that all thickening of sinus mucosa disappears after the initial acute attack, and that the nasal cavities do not have mechanical defects which obstruct sinus drainage when there is swelling of the nasal mucosa due to colds or from swimming.

4. Conserving the Patient's Time and Resources

Care should be taken to prevent waste of the patient's time and economic resources. Drastic treatment, whether medical or surgical, may make the end-result worse than the original complaints and should therefore be avoided.

PRINCIPLES OF TREATMENT OF SINUSITIS

1. *Make an accurate diagnosis.* This is done by the usual methods and checked by roentgenograms. The rhinologists of Boston are fortunate in having available the services of Dr. A. S. Macmillan, chief of the X-ray Department of the Massachusetts Eye and Ear Infirmary. The combined clinical and x-ray diagnoses have a probable positive and negative accuracy of better than 90 per cent. Although x-rays are desirable both for their immediate information as well as for later checking by comparison the end-results of treatment, they are dispensed with whenever convenience or economic reasons must be importantly considered. Poorly taken sinus roentgenograms can be very misleading; well taken but poorly interpreted films are equally so. It should be emphasized that the history and physical findings have a high degree of accuracy and should be the primary reliance both of specialists and others who deal with sinus problems.

2. *Never resort to operation,* whether major or minor, so long as adequate progress can be made by conservative treatment. While serious complications may occur from being overcautious, it must be kept in mind that ill-advised nasal surgical ventures may make the treatment literally worse than the disease.

3. It should be recognized in patients with polypoid

should be kept between 30 and 45 per cent. This is accomplished by having steam from some form of teapot going in the room for about ten minutes or so of each hour. Steam can be placed in the far corner of the room away from the patient. If the room is adequately humidified, the room temperature may be allowed to drop to 68° F.

As an adjunct to treatment, some patients are asked to *inhale unmedicated steam* for five to ten minutes every two hours when awake. A simple method of doing this is to have a thermos bottle filled with boiling water kept by the bedside. Another method is to place a quart of boiling water in a thick-walled crockery pitcher with the top of the pitcher closed by a paper bag. A small hole is torn in the corner of the bottom of the bag so that the patient may inhale steam in through his mouth and out through his nose when the mixture is very warm. After it cools somewhat, the steam is sniffed through the nose. This is an easy means for introducing both moisture and heat into the nasal cavities. *Steam may be medicated* with the following prescription:

R Camphor ʒi
95 per cent alcohol q.s. ad ʒviii
Mix and make a solution.

Sig: One teaspoonful in quart of steaming water for inhalation for five to ten minutes every two hours.

Fluids are forced to at least 3000 cc. daily. The patient is asked to use mild *laxatives* in order not to become constipated. He is told that he may eat anything easily digested which he likes—so long as his *diet* is reasonably simple. Pain, if present, is controlled by the use of *empirin* compound tablets of 6½-grain size, in a dosage of one or two tablets as often as every three hours during the day. These tablets are avoided at night because they contain small quantities of caffeine. If *aspirin* is effective, it may be employed instead of the *empirin* compound. Mild alcoholic drinks are sometimes useful in lessening pain, but whatever alcohol is taken should be well diluted with fluid. *Codeine sulfate* tablets or even stronger analgesic drugs are necessary only rarely. The writer does not employ *Dover's powder* except rarely although it is popular with many practitioners. It is not necessary to make

at the tip of a bent nasal tube much smaller than a No. 1 eustachian catheter, to withdraw ropy strands of secretion from sinus ostia by picking them up in the nasal cavity itself. This will be described with details of local treatment.

The *displacement treatment predicates* the presence of at least some air in a sinus cavity, since air itself is displaced by fluid.

TECHNIC OF LOCAL TREATMENT BY THE GENERAL PRACTITIONER

Acute Sinusitis

The patient with acute sinusitis is asked to rest as much as possible, and if he is running a temperature he is advised to go to bed. He must remain in a warm room as much of the time as possible and should not sleep in a cold room at night. If he is in bed, it is best for him to sleep long hours at night and to accomplish this purpose with mild sedatives if necessary. He is also requested to sleep for an hour or more after lunch each day. The rationale of remaining in a warm room is related to the physiological work which the nose must do in warming inspired air. Few doctors other than rhinologists realize the importance of this function or the fact that about 70,000 calories (70 large calories) go into inspired air in the adult nose daily. Sleeping in a very cold room at night with body metabolism at a low level is irrational. The patient may have all of the fresh air which he wishes so long as means are devised for warming the air before nasal respiration occurs. The *temperature of the room* should be 70° F. during the day and 60° F. during the night. Patients who insist that they are unable to sleep soundly unless the room temperature is very cold are allowed to have a night room temperature of as low as 45° F. If the patient still claims that he cannot sleep well, he is allowed to use his own pleasure in his sleeping-room arrangements. He will often tell the doctor that he has found by experimentation a great change: his nose feels better and he sleeps more soundly in a room which is merely cool rather than very cold!

Because the nose must add moisture to inspired air, an effort is made to control the *room humidity*. Relative humidity

should be kept between 30 and 45 per cent. This is accomplished by having steam from some form of teapot going in the room for about ten minutes or so of each hour. Steam can be placed in the far corner of the room away from the patient. If the room is adequately humidified, the room temperature may be allowed to drop to 68° F.

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the patient perspire freely if he has an adequate fluid intake and output other than through the skin. If he perspires very freely, he must not become chilled. This is assured by adequate nursing care or by instructing the patient to change his bed garments sufficiently to remain dry.

Sulfonamide Therapy.—The writer has frequently found in the use of sulfonamide therapy in cases of acute otitis media that accompanying acute sinusitis may improve dramatically along with the aural disease. It is very likely that sulfonamide therapy will have an important place in the future in the treatment of acute sinusitis. In the absence of any elevation of temperature, such treatment should be reserved so long as the patient makes adequate progress by time-tried methods.

Sulfadiazine is today the sulfonamide of choice and is utilized in a dosage of 0.1 gm. per kilogram per day, divided into six or eight doses. While its toxicity is relatively low as compared with some of its predecessors, very disturbing adverse effects can occur with it, such as ureteral colic from a calculus composed of sulfadiazine crystals. This very unpleasant complication has occurred in one case in the author's experience in which the fluid intake and output in an adult patient were carefully measured, the intake being above 3000 cc. per day, and the output above 1500 cc. per day. Daily blood and urine examinations were made, including complete blood counts, hemoglobin determination and sulfadiazine blood level; urinalysis was complete, including sediment for red cells and crystals. Without warning, after the patient had taken 15 gm. of sulfadiazine in forty-eight hours, he had severe ureteral colic which was relieved by the use of calcium chloride intravenously, calcium gluconate intravenously, and cystoscopy with recovery of the sulfadiazine stone from the right ureter. There were no warning red cells in the urine, no lumbar pain before the colic started, no diminished urinary output. Such cases are rare, and this one might not have occurred if the urine had been kept alkaline with the administration of sodium bicarbonate, since the sulfadiazine crystals are said (without proof) to be more soluble in an alkaline medium. Although such cases are rare, this one is

reported merely to emphasize that a powerful remedy should not be utilized except with adequate indications. The case in question had a higher degree of temperature than is usually seen in acute sinusitis, which after exhaustive study was the only explanation of the fever curve. The writer feels that because such toxicity is unusual, *sulfadiazine must occasionally be given serious consideration as a therapeutic agent in acute sinusitis*. Moreover, intractable sinus headache not controlled by ordinary methods of sinus drainage may be relieved more or less by the lessened swelling of the nasal and sinus mucous membrane which sometimes results from sulfonamide therapy.

Aqueous Nasal Sprays.—Nasal sprays are effective therapeutic agents in the home treatment of acute sinusitis. The following preparations are useful:

- B Neosynephrin hydrochloride, 0.25 per cent aqueous solution 3i
Dispense dropper in bottle.
Dispense DeVilbiss No. 15 atomizer.

Sig.: Spray both nostrils every two hours for two days; then every three hours.

The strength of the solution may be made greater—up to 1 per cent—if the nasal mucous membrane has been found by the rhinologist to shrink poorly. Other modifications include the addition of sodium chloride, grains 4; or glucose, grains 4; or, best, neosilvol, grains 6 (the convenient content of one capsule of the drug).

Ephedrine hydrochloride (less irritating to the nasal mucosa than the sulfate) may be substituted for neosynephrin in the above prescription in a strength of 1, 2 or 3 per cent; the same additional modifications may be used. The very bitter taste of an ephedrine salt may be easily disguised by saccharin, grain $\frac{1}{4}$ or grain $\frac{1}{2}$ to an ounce of solution. Alternative substitutions for neosynephrin are 1 per cent propadrine hydrochloride or 1 per cent paredrine hydrobromide.

A benzedrine inhaler is sometimes found useful in shrinking the nasal mucosa.

It may be desirable to spray the nose more frequently or less so, depending on the patient's response to the foregoing.

Cocaine is a powerful and potentially toxic, habit-forming drug. It must especially be respected when dispensed in aqueous (i.e., relatively rapidly absorbed) solutions. However, this drug potentiates the action of adrenergic stimulants, and may be added to the ephedrine or neosynephrin prescriptions described above if strongly indicated. While cocaine muriate

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Incidentally, the thought enters one's mind as to why the swallowing of liquid petrolatum routinely by enormous numbers of the laity for chronic constipation has not resulted in more reports of pulmonary damage.

While the danger of oil aspiration from nasal treatment has probably been overemphasized, certain pertinent facts must be accepted: (a) *Liquid petrolatum* in the tracheobronchial tree is a harmful agent. (b) Certain vegetable oils have been known to do serious harm; for example, the tracheal instillation of *lipiodol* for treatment in asthma cases. (c) Cannon³ accepts *olive oil*, *cottonseed oil*, *sesame oil*, and *poppyseed oil* as relatively nontoxic. (d) Liquid petrolatum should never be used in such manner as seriously to risk passing the "valve" of the glottis. Thus such oil would be extremely dangerous in a screaming, crying child, and in general had best be omitted in young children. Patients in later life frequently have poor glottic reflexes and should not be given liquid petrolatum. Moreover, nasal oils should be withheld for an hour or more before sleeping, when the glottic reflex becomes less likely to reject the oil.

With these precautions, the author is willing to recommend the following prescriptions. Rhinologists may, of course, substitute one of the above-mentioned vegetable oils for the liquid petrolatum base. These prescriptions should be used in an atomizer which makes a very finely divided spray (such as DeVilbiss No. 14), and should be employed sparingly so that the total dosage may remain small.

R Cocaine alkaloid gr. vi
Chlorethane inhalant ad 5ii

Sig.: Spray both nostrils not more often than every two hours.

R Camphor gr. ss
Petrolatum, liquid (light) ad 5i

Sig.: Spray both nostrils five minutes after using watery nasal spray.

The first of these two prescriptions may be used as an alternative to the adrenergic watery nasal sprays described above. It has the advantage of having minimal cocaine absorption by use of an oily vehicle, i.e., oil solutions make for slow absorption, but adequate local action occurs.

(or other salts of cocaine) has no adverse effect upon the cilia of the nasal mucosa even in 2 per cent solution, ordinarily 0.5 per cent or 0.25 per cent will reinforce sufficiently the effectiveness of the preparations discussed.

These are all aqueous solutions without effect upon normal ciliary streaming which is the normal mechanism for self-cleansing of the nose and sinuses by the pseudostratified ciliated columnar epithelium. Proetz² stresses the fact that ciliary function continues in the presence of infection. Drying, ill-advised traumatic treatment, poor selection of nasal medications (e.g., 1:1000 adrenalin hydrochloride or very strong cocaine solution, instillation of large doses of dry powdered sulfonamide, 5 per cent sodium sulfathiazole,⁷ etc., into the nasal cavities) may inhibit or temporarily destroy ciliary action.

Caution should be employed in using any adrenergic drug (such as neosynephrin or ephedrine) *in patients having cardiovascular disease or hypertension*, and in such cases these drugs must be utilized in the weakest effective solutions, and at the widest possible intervals. Ephedrine salts are said to have an action period of three hours or less on the nasal mucosa.

Oily Nasal Sprays.—Since effective aqueous nasal medications are now available, the desirability of the use of *nasal oils* is questionable. Cannon³ has emphasized that nearly 200 cases of oil aspiration pneumonia have been reported, of which 105 cases, mostly discovered at necropsy, were in adults. Of the adult cases, 20 per cent were acquired because of intranasal medication, while in a series including infants, children and adults reviewed by the same author, about one third resulted from the use of intranasal oils. In considering the total groups of cases, it should be kept in mind that every type of fatty substance entering the throats of all people of all ages and states of health and disease has resulted in this incidence of proved cases. In adults, a rate of 20 per cent of 105 cases would mean twenty-one cases of pneumonia due to nasal medication. When one realizes that tens of millions of adults have in the past used oily nasal medicaments, the twenty-one cases become less impressive.

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The second preparation allays the sensation of dryness of which patients occasionally complain in both the nose and throat, especially the latter, when aqueous solutions alone are used for spraying the nose. It may be used in conjunction with the ephedrine, neosynephrin and other preparations described above, the latter being employed first and the camphorated oil a few minutes later.

There is no proof that liquid petrolatum impairs ciliary motion. Since an oil will not mix with the watery mucous blanket which overlies the cilia, the propulsive action of this blanket is said to be rendered less effective.²

TECHNIC OF LOCAL TREATMENT BY THE RHINOLOGIST

Acute Sinusitis

The specialist must always bear in mind the fact that he is dealing with extremely delicate membranes and that his most valuable allies in getting the patient well are the cilia of the nasal cavities and sinuses. The purpose of treatment is to produce normal ciliary action or to stimulate such action and to relieve the equivalent of hour-glass constrictions near the nasal or sinus side of the sinus ostia. Anatomically, the normal ostium may be actually a tunnel as is frequently seen in anatomical specimens of normal antral ostia.

Nasal Tamponade.—The shrinking of the mucosa around the ostia may be accomplished by the use of one of the adrenergic drugs mentioned above, especially *neosynephrine hydrochloride* in 0.25 per cent aqueous solution or *ephedrine hydrochloride* in 2 per cent aqueous solution. The writer prefers thin, small, soft, long-fiber cotton tampons made quite wet and placed very gently in the middle meatus. After these have remained in situ for a few minutes, they are replaced by additional tampons soaked with the same chemical but also containing very weak colloidal silver-protein in the form of silver iodide gelatin. (Lierle and Moore⁴ have reported an initial speeding of ciliary activity from mild silver-protein action.) These are left in situ for about a half an hour or even somewhat longer if they are easily tolerated by the patient.

It is felt that aside from being nonirritating to the nasal mucosa, these tampons tend to produce a flow of mucus not only from the nasal mucosa but from the sinus ostia near which they are placed, by their simple action as foreign bodies. The term "packing of the nasal cavities" is a poor one, since such tampons should not exert pressure, but should be gently invaginated into the nasal cavities without pressure and without trauma of any kind. The utmost gentleness should be employed, otherwise the tampons do more harm than good. Most observers agree that such tampons are associated in many cases with a profuse flow of nasal mucus. There is some question as to the exact origin of the mucus. It is likely that at least some of the mucus comes from secretion on the nasal side of the sinus ostium, and in some cases undoubtedly comes from the sinus side of the ostium.

Aspiration of Mucus; Irrigations.—After removal of the tampons, a slender nasal suction tip with a negative pressure of 3 to 4 pounds is utilized to aspirate, especially from the region of the middle meatus, the resulting discharge. The tip of the suction tube does not actually touch the nasal mucosa, but comes in contact only with secretion. The excess far back in the nose can frequently be picked up as actual ropes of mucus draining from one or more sinus ostia; the tenacious quality of such ropes may permit the withdrawal of important amounts of secretion from the sinuses into the nose when "spot" suction is applied in the nasal cavity near sinus ostia.

In patients having very acute sinusitis with thin nasal discharge or simple purulent discharge, such ropy secretion does not, of course, occur. Sometimes small dried inspissated masses of secretion are found acting as plugs to sinus drainage. These are removed. In patients having *allergy*, the character of the discharge may be very viscous and require much stronger negative pressure, but under no circumstances should the suction tip be allowed to touch the nasal mucosa or traumatize it in any way.

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solution used for the nasal tamponade are then instilled into each middle meatus, and superior meatus if necessary, under gentle positive pressure with a Luer syringe to which is attached a long, very small, easily bent, silver cannula. This same cannula can be used for irrigation of the antrum through its normal ostium in favorable cases, but it is felt that such irrigation is only rarely necessary with the treatment being described.

It must be emphasized that the positive pressure is directed *laterally* against the *lateral* nasal wall and is designed not to fill sinuses but to clear their ostia. If a suspension of the irrigating solution is made by mixing it with the camphorated oil mentioned above or a vegetable oil, empirically a greater quantity of mucus is obtained.

The use of gentle positive pressure as described above against the lateral nasal wall must be accompanied by certain *precautions*. The stream must be directed *laterally*, not posteriorly; the patient must hold his breath (*i.e.*, close the glottis) while the solution is being instilled; after rapid instillation he must lean quickly forward and allow the excess medication to drain anteriorly into a basin so that he will avoid coughing; etc. The nasopharynx must be aspirated of all secretion before the instillation of the fluid so as to protect the eustachian tube from having such secretion possibly coughed into it. If the treatment is skillfully done, no cough will result. Moreover, the writer has never personally seen any involvement of the middle ear from such therapy, or any pulmonary damage.

It must be further emphasized that this technic does not carry with it the risks of massive nasal douching. It is felt by the writer to be more easily controllable than the vacuum displacement method, in that normal sinuses are not jeopardized by it, even though it is said to be impossible to infect normal sinuses by displacement.

This type of treatment is repeated every two or three days for about five days, after which the patient has usually improved sufficiently to get along satisfactorily with the home treatment prescribed above for an additional five days. Thereafter, the treatment is continued at about weekly intervals

until the clinical condition is satisfactory and comparative sinus x-rays are found to be normal.

Ultra short-wave diathermy may be applied through the affected sinus or sinuses while the tampons remain in the nose or after they have been removed provided the resulting hyperemia of the nasal and sinus mucosa does not tend to obstruct sinus drainage and undo the fundamental aims of local treatment which are to establish drainage and allow sinus ventilation.

Results of Treatment.—The most rapid resolution which the writer has observed of acute unilateral pansinusitis is twelve days from the onset of symptoms and treatment to apparently complete resolution, although the patient still had very slightly thickened membrane in the antrum and ethmoid by x-ray examination at the end of the twelve days. A similar patient recovered completely in two and one-half weeks from a clinical and x-ray examination showing pus in all sinuses on one side to complete resolution without residual thickened membrane. The average period of resolution by x-ray, according to Dr. A. S. Macmillan, is three to four weeks. The patient usually thinks that he is over his illness in about seven to fourteen days, averaging nearer ten days. The thickened sinus mucosa persists usually for about two to four weeks after the patient himself thinks he is "cured," and acts as a predisposing cause for a recurrence of symptoms if chilling, severe fatigue, or gross transfer of infection from someone else occurs.

Subacute Sinusitis

- The medical treatment of subacute sinusitis follows more or less the same pattern as that described for acute sinusitis except that the severe malaise which accompanies the latter disease is less of a problem, and less symptomatic supportive therapy is needed. The majority of such cases, especially those who have had little or no medical attention during the acute phase of their illness, develop a secondary anemia which is easily demonstrated if the physician takes the trouble to look for it. In such patients, the use of a "tonic" of iron, liver and vitamin B ("lextron" capsules are a useful prepara-

tion in a dosage of one with each meal for four weeks) offers definite assistance.

Chronic Sinusitis

With chronic sinus disease, the same problems of *drainage* and *aeration* are paramount.

Operative Treatment.—A large group of rhinologists, upon establishing a diagnosis of chronic sinusitis, immediately advise operation. Naturally, the patient expects real benefit or cure to result, just as when his appendix was removed. This expectation has led to disappointment in a sufficiently large group of cases throughout North America to cause the laity to regard any form of sinus surgery with apprehension. On the other hand, brilliant results of certain such operations, especially with disease limited to the antrum, have been obtained.

Since it is not possible to excise a sinus completely without leaving at least a portion of its shell to become reinfected or grow polypoid tissue, and since the preservation of normal nasal physiology is of paramount importance in the majority of uncomplicated cases of chronic sinusitis, a plan of treatment must be worked out which will yield satisfaction to both doctor and patient. Each patient becomes a special problem and some of the following suggestions may prove helpful:

Tell the patient *before any surgery is done* that an operation may be followed by recurrence of the sinusitis and that *prevention* after such an operation must be carried out. Such prevention means the avoidance of acute upper respiratory infection so far as possible. Prolonged chilling and severe fatigue should not be tolerated. The patient's general health should be looked after so that his well-being is constantly satisfactory. Skillfully used coagulation diathermy (not desiccation) can control a tendency toward recurrences of polypoid tissue. Simple purulent sinusitis, once well, may never recur.

If circumstances allow it, treat the chronic sinus disease conservatively for a limited period of time, for example, six weeks, and compare the clinical and sinus x-ray examinations

before and after such treatment to see what progress has been made. Sufficient regression may occur to rule out the desirability of a surgical approach.

If the sinusitis is *polypoid*, do not rely upon the control of allergy for fundamental improvement, because in these particular cases such therapy is only occasionally successful in the nose and sinuses. Polyps should ordinarily be removed; occasionally they will disappear with the subsidence of an acute or subacute exacerbation of infection (but recur with a subsequent flare-up) having no relationship to allergy. On the other hand, the removal of an allergen, or desensitization to it, may have similar but less striking results. Hansel⁵ believes *very weak* house-dust inoculations to be of much value in certain cases.

The *principles and technic* of surgical treatment of sinusitis are beyond the scope of this paper, but certain simple fundamentals should be mentioned. The first is that correction of the septum, resection of the anterior tips of the middle turbinates, excision of nasal polyps, and making certain that the nasal mucosa functions physiologically but without obstructing nasal respiration (especially in cases of vasomotor rhinitis with associated sinusitis) offer a reasonable hope that sinus surgery may be avoided. When such surgery is engaged upon, however, it should be of the most conservative variety, with such procedures limited to skillful intranasal techniques of antrum and ethmoid drainage so far as possible. It is always easy to do more drastic work at a later date if necessary, and conservatism is frequently accompanied by very pleasant surprises for both patient and doctor.

Chemotherapy.—In chronic purulent sinusitis due to gram-positive organisms, it is possible that *gramicidin* will prove to be a valuable therapeutic agent at some time in the future, judging by its preliminary, carefully controlled trials. More must be known about its possible clinical toxicity before it can be generally employed.

The writer has recently observed a case in whom there was extremely severe bilateral polypoid pansinusitis in spite of multiple previous operations to control the disease. After such observations were made, the patient, who lived in a dis-

tant city, was not seen for a number of weeks. When she returned, her nose was found to be astonishingly improved. The history which she gave was that she had had an acute otitis media which had been treated by paracentesis and large doses of *sulfathiazole* by mouth. She had observed immediate symptomatic improvement in the condition of her nose. Another patient who received sulfonamide treatment for about a week in adequate dosage by mouth for incipient mastoiditis, not only recovered from his aural disease but also had remarkable improvement in his accompanying bilateral purulent and polypoid pansinusitis. This improvement continued during more than a year's follow-up. These cases suggest that sulfonamide therapy by mouth may be useful in selected cases of chronic sinus disease.

Lyons⁶ has investigated this possibility and has stated that *sulfadiazine* is helpful in chronic sinusitis cases not yielding to other treatment if the infection is due to a hemolytic streptococcus or pneumococcus (not staphylococcus) and if adequate antibodies are present or supplied to the patient. An acute exacerbation of nasal infection, however, usually produces a relapse in the chronic disease.

Lues should always be excluded in the differential diagnosis of chronic sinusitis. The treatment of syphilis may be accompanied by marked regression or cure of the sinus pathology.

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THE TREATMENT OF THE INFECTIOUS ARTHRITIDES WITH SULFONAMIDE COMPOUNDS*

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THE dramatic alteration in the clinical course of many of the specific infectious arthritides following the administration of sulfanilamide or one of its related compounds is adequate evidence in itself that these drugs exert a specific chemotherapeutic effect on the causative organisms. The results have been so striking that one is forced to conclude that the advent of the sulfonamide compounds represents the greatest advance ever made in the treatment of joint disease. In the space at our disposal for this clinic we shall discuss the treatment of the arthritides affected favorably by these chemotherapeutic agents. In addition, we shall refer briefly to those types of arthritis in which sulfonamide therapy is of questionable value, ineffective, or not yet established. We shall attempt, wherever possible, to present case records illustrating the therapeutic effectiveness of the drug administered.

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THE DIAGNOSIS OF THE SPECIFIC INFECTIOUS ARTHRITIDES

The prime requisite for good therapy is to make a correct diagnosis as soon as possible. This is of extreme importance especially in cases of specific infectious arthritis that respond favorably to the sulfonamide compounds, since the earlier chemotherapy is instituted, the more dramatic are the results. Furthermore, if such specific therapy is not administered before the end of the third week, irreparable damage to the involved articulations will have taken place in a fair number of cases.

The diagnosis of the specific infectious arthritis is, as a rule, relatively straightforward and simple. These types of arthritis are the direct result of invasion of the articular structures by a specific organism. The organisms, in most instances, reach the joints via the blood stream. In a large percentage of the cases, with the exception of tuberculosis and syphilis, the blood stream invasion will be accompanied by a chill, chilly sensation and fever. The *onset* of infectious arthritis is almost always acute. It is frequently characterized during the early phase of the disease by polyarticular arthritis or aches and pains which are migratory in nature. Within a few days the arthritis is confined to one or more joints, usually large ones, although no joint is exempt. The joints involved are acutely inflamed and usually very painful. Joint effusions are generally present. This type of onset is rarely encountered in any other type of acute arthritis.

Once one suspects the presence of an acute infectious arthritis, he must next determine the *type* if possible. A reliable *history* is oftentimes most helpful in suggesting not only the type of arthritis present, but also the portal of entry of the offending organism. Because gonococcal arthritis is more common than the other forms of the disease, particularly in adults, this possibility should be suspected during the anamnesis.

Physical examination may reveal the presence of a primary focus such as osteomyelitis, a boil or abscess, pneumonia, endocarditis, or a genito-urinary tract infection. *Roentgenograms* made during the first two weeks of the disease do not reveal bony or cartilaginous changes, unless a neighboring

focus of osteomyelitis is present. *Bacteriological tests*, including the various agglutination and complement fixation tests as well as cultures of blood, synovial fluid and suspected foci, should be made whenever possible.

When joint effusions are present, early diagnosis is often possible by *aspiration and examination of the synovial fluid*. Cultural methods are far superior to attempted demonstration of the organisms in stained smears. Fluids in infectious arthritis are usually cloudy and generally clot on standing. Fluids with positive cultures rarely contain less than 30,000 leukocytes per cu. mm., 90 per cent of the leukocytes being polymorphonuclear; the sugar content is greatly reduced or absent; the mucin is decreased in amount and precipitates poorly, leaving a cloudy or hazy supernatant fluid; the percentage concentration of total proteins approximates that contained in the serum.

TYPES OF SPECIFIC INFECTIOUS ARTHRITIDES WHICH RESPOND TO THE SULFONAMIDES

We shall first discuss those specific infectious arthritides which are favorably influenced by sulfanilamide and its allied compounds. The drugs of preference and adequate dosages are shown in the accompanying table.

1. Gonococcal Arthritis

In the past, gonococcal arthritis caused joint destruction and some degree of permanent disability in approximately 25 per cent of the cases. Experience with the sulfonamide compounds has taught us that these disabilities should rarely, if ever, occur in the future, provided the correct diagnosis is made early and the sulfonamide drug of choice is administered in adequate doses soon after the diagnosis is made. Gonococci within the articular cavity are more susceptible to sulfonamide compounds than are the same organisms in the genito-urinary focus. This probably signifies that the genito-urinary tract is a more favorable habitat for the gonococcus than an articular cavity and probably explains why the genito-urinary focus may persist occasionally even though the arthritis has been cured.

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should be performed and may be expected to be positive in at least 85 per cent of the cases of gonorrheal arthritis. This test should never be relied upon except as a corroborative or suggestive diagnostic test.

After having established a positive or presumptive diagnosis of gonococcal arthritis, specific therapy should be instituted immediately. The only *contraindication* to the immediate administration of one of the sulfonamide drugs to a patient with gonococcal arthritis is the presence of known sensitivity to the drug or complications such as liver disease, a blood dyscrasia, or severe renal disease. The drug may be given in the last case provided too high a concentration in the blood, because of impaired renal excretion, is avoided by frequent determinations of the blood level.

In our experience, the *treatment* of gonococcal arthritis with sulfanilamide is fully as effective as with any of the other sulfonamide compounds, provided blood levels of 10 to 15 mg. per 100 cc. are maintained for a period of at least one week. The dramatic clinical response which ensues following its administration is illustrated in the following case report.

CASE I.—Mrs. E. S., a twenty-four-year-old housewife, developed leukorrhea two weeks before admission to the hospital. Four days after onset of leukorrhea, she had a severe chill followed by a temperature of 104° F. and subsequently developed headache and severe pain in the jaws, neck and lower back. Two days later, the left knee became acutely painful, swollen and hot.

The patient had no history of previous illnesses except for an attack of rheumatic fever at the age of ten years.

The physical examination on admission revealed redness and swelling of the left knee and profuse vaginal discharge. Immobilization by means of a cast, and opiates were necessary to ease the pain in the knee. The temperature ranged from 100° F. to 102° F. The leukocyte count was 15,000 per cu. mm., 79 per cent of the cells being polymorphonuclears. The synovial fluid had a white cell count of 41,000 per cu. mm., 98 per cent being polymorphonuclears, a sugar content of 29 mg. per 100 cc., and a culture positive for gonococci.

Forty-eight hours after sulfanilamide therapy was instituted (90 grains a day), opiates and cast were no longer necessary and 30 degrees of painless motion of the knee was possible. At this

TABULATION

THE DRUG OF PREFERENCE AND THE DOSAGE EMPLOYED IN VARIOUS TYPES OF ARTHRITIS

Causative Organism	Drug of Choice	Dose (Gm. per day)	Desired Blood Level (Mg. per cent)
Gonococcus.....	1st Sulfathiazole 2nd Sulfanilamide	6-8 6-8	3-8 10+
Streptococcus hemolyticus.....	1st Sulfadiazine 2nd Sulfanilamide	6-8 6-8	10-15 10+
Staphylococcus...	1st Sulfathiazole 2nd Sulfapyridine	6-8 6-8	3-8 3-5
Meningococcus ..	1st Sulfadiazine 2nd Sulfanilamide	6-8 6-8	10-15 10+
Colon bacillus ...	1st Sulfadiazine* 2nd Sulfathiazole	6-8 6-8	10-15 3-8
Pneumococcus	1st Sulfadiazine 2nd Sulfathiazole	6-8 6-8	10-15 3-8

* Sulfathiazole is probably more effective than sulfadiazine in treating colon bacillus infections, but the latter is less toxic.

A *positive diagnosis* of gonococcal arthritis can be made only by aspiration of the joint and demonstration of the gonococci. A *presumptive diagnosis*, and one that is usually sufficient for clinical purposes, may be made by finding a genito-urinary focus in a patient with a history of joint disease compatible with gonorrheal arthritis. If gonococci cannot be demonstrated in the suspected focus, one is forced to rely upon a history and/or physical findings indicating a previous gonococcal infection. One should always make repeated attempts to demonstrate the presence of gonococci. Smears and cultures should be obtained, from the urethral and prostatic fluids in the case of the male and from the vagina, cervix, Bartholin's and Skene's glands in the female, on at least three successive occasions. If these smears and cultures fail to show the presence of gonococci, the use of a provocative gonorrheal vaccine may occasionally result in obtaining positive smears and cultures twenty-four to forty-eight hours after injection. In addition, a gonococcal complement fixation test

should be performed and may be expected to be positive in at least 85 per cent of the cases of gonorrheal arthritis. This test should never be relied upon except as a corroborative or suggestive diagnostic test.

After having established a positive or presumptive diagnosis of gonococcal arthritis, specific therapy should be instituted immediately. The only *contraindication* to the immediate administration of one of the sulfonamide drugs to a patient with gonococcal arthritis is the presence of known sensitivity to the drug or complications such as liver disease, a blood dyscrasia, or severe renal disease. The drug may be given in the last case provided too high a concentration in the blood, because of impaired renal excretion, is avoided by frequent determinations of the blood level.

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The physical examination on admission revealed redness and swelling of the left knee and profuse vaginal discharge. Immobilization by means of a cast, and opiates were necessary to ease the pain in the knee. The temperature ranged from 100° F. to 102° F. The leukocyte count was 15,000 per cu. mm., 79 per cent of the cells being polymorphonuclears. The synovial fluid had a white cell count of 41,000 per cu. mm., 98 per cent being polymorphonuclears, a sugar content of 29 mg. per 100 cc., and a culture positive for gonococci.

Forty-eight hours after sulfanilamide therapy was instituted (90 grains a day), opiates and cast were no longer necessary and 30 degrees of painless motion of the knee was possible. At this

time the synovial fluid had become sterile, the leukocyte count had fallen to 13,200 (98 per cent polymorphonuclears), and the sugar content had risen to 82 mg. Cervical smears became negative for gonococci on the second day of treatment. The gonococcal complement fixation test never became positive. On the seventh day of treatment, only 2 cc. of fluid could be aspirated from the knee and the leukocyte count was 1000 with 6 per cent polymorphonuclears.

Two weeks following the beginning of therapy, the motions of the knee were normal and weight-bearing was possible. The initial sedimentation rate of 1.69 mm. per minute fell to 0.79 mm. three weeks later and to 0.29 mm. twelve weeks later. During the forty-six-week follow-up period, the patient remained well and all laboratory tests gave normal findings.

Summary: In a severe case of proved acute gonorrheal arthritis, in which persistent joint damage would probably have resulted under former methods of treatment, adequate doses of sulfanilamide produced an excellent response with no residual limitation of joint motion.

The administration of sulfanilamide, in the amounts necessary to maintain an adequate level of the drug in the blood stream is productive of cyanosis, nausea, vomiting, headache, dizziness, anemia, leukopenia, agranulocytosis and hepatic damage in a far larger percentage of patients than is the case with the related drugs. Although hematuria occurs frequently following the administration of both sulfapyridine and sulfathiazole, the latter causes much less nausea and vomiting. Therefore, the sulfonamide of choice is sulfathiazole, even though skin rashes are more commonly encountered following its administration. If sulfadiazine should prove to be equally efficacious in the treatment of the disease, it will probably be the drug of choice because it is well tolerated and results in a minimum of toxic manifestations.

When treating gonococcal arthritis with *sulfathiazole*, it is our practice to administer 2 gm. as the initial dose, repeat in four hours, and follow by 1 gm. every four hours day and night. We aim to maintain a fluid intake of 2500 cc. every twenty-four hours or the amount necessary to insure a daily urine output of 1000 cc. Hemoglobin content and

leukocyte count should be determined every third day. A urine analysis should be made each day, watching especially for microscopic hematuria. The blood concentration of the compound should be determined every second or third day. In most instances a blood level of 3 to 6 mg. per 100 cc. is adequate. When patients suffering with gonococcal arthritis are treated with sulfathiazole in this manner, results equally as dramatic as with sulfanilamide are observed, as is shown in Case II.

CASE II.—Mr. H. B., a twenty-nine-year-old mechanic, developed a urethral discharge one month before being admitted to the hospital. One week following onset of the discharge, he noted stiffness and pain in the left shoulder, neck and right knee. A conjunctivitis and a skin eruption confined to axillae, groins and soles of feet appeared at the same time. Sulfanilamide, in doses of 1 to 2 gm. a day, was given for two weeks without effect.

The past history was irrelevant to his present illness except for an attack of gonorrhea eleven years before admission.

Physical examination showed that there was tenderness of the left acromioclavicular joint, moderate limitation of neck motions, tenderness and swelling of both knees. There were numerous, red, slightly elevated, crusted lesions in both axillae and groins and over lower legs and feet. Temperature was 100° F. There were 21,600 leukocytes per cu. mm. of blood, 78 per cent being polymorphonuclears.

Sulfathiazole treatment was started with an initial dose of 4 gm., followed in two hours by 2 gm., and after that 1 gm. every four hours for three days. Subjective improvement was apparent within forty-eight hours, and the joint swelling and tenderness subsided gradually during the following three weeks.

Summary: A case of probable gonorrheal arthritis and keratoderma blenorrhagicum, that had shown no tendency to improve spontaneously, responded to treatment with full dosages of sulfathiazole.

Striking improvement similar to that in the case just summarized has been observed in the few patients we have treated with full dosages of *sulfadiazine*. This is illustrated in Case III.

CASE III.—Mr. J. C., a fifty-five-year-old, unmarried houseman, was admitted to the hospital. Five days before admission, the patient had a severe respiratory infection with substernal pain and a productive cough. Three days before entry, he noted gradual onset of pain and swelling in the left knee, the swelling and pain increasing steadily up to the time of admission. At no time did he have genito-urinary symptoms.

The past history was irrelevant to his present illness except for dysuria for three weeks twenty-five years before entry.

On admission, the left knee was extremely tender, hot and swollen and was held in 15 degrees of flexion. Temperature was 101° F.; white blood cell count was 19,000 per cu. mm. Culture of the fluid from the left knee was positive for gonococci. Sulfadiazine was given for fifteen days in doses of 4 gm. a day with a resulting blood level up to 10 mg. per 100 cc. There was marked improvement in the left knee within forty-eight hours after treatment was started and in two weeks the pain and swelling had subsided and the patient was ambulatory.

Summary: Recovery in this case of proved acute gonorrheal arthritis occurred rapidly with sulfadiazine therapy.

As can be seen from the following abstract of a clinical history, patients with probable gonococcal arthritis respond to *sulfanilamide* fully as well as do those with a proved arthritis.

CASE IV.—Mr. N. K., a twenty-four-year-old, married shoe worker, developed urethral discharge, after sexual exposure, five months before admission to the hospital. At approximately the same time as the onset of the urethral discharge, the patient injured his right hand and the second metacarpophalangeal joint became red, swollen and painful. Within the following week, the third left metacarpophalangeal joint and both heels became painful and swollen. One month later, both ankles were involved and subsequently both knees became painful, tender and swollen. He was treated by his local physician with "white pills" in two courses of nine days each. During this time, the urethral discharge disappeared but the joint symptoms continued and patient noted increase in malaise and anorexia.

The past history was noncontributory to the present illness.

The physical examination on admission showed no abnormalities except for the joint findings. The second metacarpophalangeal joint on the right and the third metacarpophalangeal joint on the left were swollen and painful; both knees were swollen and tender, the right knee containing a definite effusion; right ankle and right third metatarsophalangeal joint were swollen and tender. Temperature was 99.6° F., pulse rate 100.

The leukocyte count was 10,000 per cu. mm., with 50 per cent of the cells polymorphonuclears. Cultures of prostatic secretion were positive for gonococci. Synovial fluid, aspirated from the right knee, contained 8000 white cells per cu. mm., 70 per cent of which were polymorphonuclears. X-rays showed mottled atrophy of the bones of the right knee and of the left tarsal and metatarsal bones and periosteal new bone formation on the head of the second right metacarpal.

The patient was given a two weeks' course of sulfanilamide treatment, receiving 8 gm. a day for the first nine days and 6 gm. a day for the remainder of the period, with a resulting blood level up to 16.7 mg. per 100 cc. Slight reduction in the swelling and tenderness of the metacarpophalangeal and of the metatarsophalangeal joints was apparent in forty-eight hours. Thereafter, there was steady, gradual improvement in all of the joints and, in two weeks, the only joint symptoms were occasional pains in the knees and ankles; slight swelling of the right knee and right ankle persisted. Prostatic smear was negative for gonococci three days after treatment was begun. The only toxic symptoms resulting from the ingestion of sulfanilamide were slight euphoria and a decrease in red count from 4,000,000 cells per cu. mm. to 3,500,000.

Summary: Adequate doses of sulfanilamide produced rapid improvement in a patient with gonorrheal urethritis and probable subacute gonorrheal arthritis.

In cases of probable gonococcal arthritis the response to therapy is of diagnostic significance. Therapeutic tests are always justified in any case of arthritis which might possibly be due to the gonococcus. Improvement of chronic gonorrheal arthritis of six to twelve weeks' duration is never dramatic.

The sedimentation rate falls rapidly in those cases of gonococcal arthritis showing striking clinical improvement.

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fadiazine, sulfapyridine treatment was instituted. The patient received 6 gm. a day for six days with a resulting blood level of 3.6 mg. per 100 cc. At the end of this period the drug had to be discontinued because of apparent sensitivity, evidenced by a temperature of 103° F. During the course of sulfapyridine therapy there was a slight improvement of the joints and the urethral discharge seemed to be decreasing. However, when the medication was discontinued, the discharge increased, the prostate became larger and more tender and the patient developed urinary retention. Simultaneously, there was increased pain, swelling and tenderness of the fifth metatarsophalangeal joint on the right.

Because of the failure of the other three sulfonamide compounds, sulfanilamide treatment was started and doses of 10 gm. a day were given for ten days, with a resulting blood level up to 14 mg. per 100 cc. During this treatment, the urethral discharge continued and the patient developed epididymitis. At first the metatarsophalangeal joint improved slightly, but later became more painful as did the left knee.

Since the only indication of any response to chemotherapy had occurred under sulfapyridine treatment, it was decided to repeat this therapy. The fever, previously interpreted as sensitivity to sulfapyridine, had apparently represented a reaction to the formation of a prostatic abscess. The second course of sulfapyridine was continued for six weeks, with doses of 6 to 8 gm. a day, and with a blood level up to 7.8 mg. per 100 cc. During this period, the urethral discharge continued and the joints showed slight improvement at first but later became definitely worse, increased pain, most marked in the heels, right ankle and hips, being manifest. An attempt was made to combine fever therapy with the sulfapyridine treatment, but the patient did not tolerate fever well. It was apparent that chemotherapy had not affected the course of the disease and further treatment was limited to hot sitz baths and irrigations. The urethral discharge finally cleared, the joints became normal, and prostatic cultures became negative for gonococci three and one-half months after admission to the hospital. The patient has remained essentially symptom-free and prostatic cultures have remained negative during the four months of follow-up.

Summary: Sulfathiazole, sulfadiazine, sulfapyridine and sulfanilamide all failed to produce any effect in this case of probable acute gonorrheal arthritis and urethritis.

whereas patients improving slowly exhibit a correspondingly slower fall in the sedimentation rate. Thus, it would appear that a rapid fall in the sedimentation rate is indicative of a satisfactory response to the dose of the drug being administered.

The gonococcal complement fixation test may fail to become positive if treatment is started while the test is still negative. In the majority of cases it will become negative within a few months after institution of therapy.

The following case report illustrates clearly a fact that has been observed by many workers, namely, that *a small percentage of patients having gonococcal infections are not cured*, even though the sulfonamide compounds are administered in adequate doses over long periods of time.

CASE V.—Mr. R. W., a twenty-nine-year-old, single milkman, noted a profuse urethral discharge following sexual exposure, seven days before admission to the hospital. On the fourth day of the discharge low back pain developed and on the following day the left ankle became swollen, red and acutely tender. The next day intermittent chills and fever appeared.

The patient's past history was irrelevant except for an attack of gonococcal urethritis followed by arthritis of the left ankle eight years before admission.

Physical examination revealed slight conjunctival injection, profuse urethral discharge, marked swelling, redness and tenderness of the left ankle and slight tenderness in the region of the lower lumbar spine. Temperature ranged from 100° F. to 102° F., pulse rate was 100. Leukocyte count was 9000 to 11,000 cells per cu. mm. Prostatic smears and cultures were positive for gonococci.

Sulfathiazole treatment, with doses of 6 gm. a day and a blood level up to 4.8 mg. per cent, was given for nine days. During this time the patient developed pain in the fifth metatarsophalangeal joint on the right; the urethral discharge was unaffected by the medication. The treatment was, therefore, changed to sulfadiazine, and doses of 5 to 8 gm. of this compound were given per day for seven days, with a resulting blood level up to 8.3 mg. per cent.

Because the left knee became involved and the urethral discharge continued while the patient was being treated with sul-

radiazine, sulfapyridine treatment was instituted. The patient received 6 gm. a day for six days with a resulting blood level of 3.6 mg. per 100 cc. At the end of this period the drug had to be discontinued because of apparent sensitivity, evidenced by a temperature of 103° F. During the course of sulfapyridine therapy there was a slight improvement of the joints and the urethral discharge seemed to be decreasing. However, when the medication was discontinued, the discharge increased, the prostate became larger and more tender and the patient developed urinary retention. Simultaneously, there was increased pain, swelling and tenderness of the fifth metatarsophalangeal joint on the right.

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Summary: Sulfathiazole, sulfadiazine, sulfapyridine and sulfanilamide all failed to produce any effect in this case of probable acute gonorrheal arthritis and urethritis.

Whether failures similar to those in the preceding case represent sulfonamide-resistant gonococcal strains, or some inherent host factors which fail to play their usual role, is unknown. Partial evidence favoring either theory is at hand. There is reason to believe that previous small doses, insufficient to cure the gonococcal infection, may increase the resistance of the organism to subsequent large doses of the sulfonamides. Further studies are necessary before these and other questions can be answered. Our present working rule is to try sulfanilamide in instances of "sulfathiazole failure." If the case proves to be sulfanilamide-resistant, we then resort to sulfadiazine and, finally, to sulfapyridine. If each of the chemotherapeutic agents is without effect, we then employ fever therapy with or without sulfathiazole or sulfadiazine. Our experience with such failures has been so limited that we are not in a position to speak concerning the advantages of one form of therapy as compared to another.

In an occasional patient having a residual genito-urinary focus following the administration of large doses of the sulfonamide drugs, we have resorted to *local therapy*, in most instances using 10 per cent neosilvol urethral instillations three times a day. When indicated, *prostatic massage* has been employed in conjunction with the local therapy. In cases in which it takes weeks or months to obtain a cure, it is always difficult to know whether to ascribe the improvement to the therapy employed or to look upon it as a natural cure.

Available data pertaining to the treatment of uncomplicated gonorrhea do not prove that there is any merit in the combined therapy over treatment with the chemotherapeutic agent alone. Eventually further studies will prove whether or not the combination of local treatment and one of the chemotherapeutic drugs is advantageous. Certainly, there is no contraindication to this therapy.

2. Streptococcal Arthritis

Like other organs in the body, the joints may be infected by pyogenic organisms, the most common being the *Streptococcus hemolyticus*. The organism may reach the articular cavity through the blood stream, by extension from a neigh-

boring focus of osteomyelitis, or from the outside by a penetrating wound. With specific chemotherapeutic agents at hand to treat such bacterial infections, it is most important to establish an etiologic diagnosis. In articular infections due to the *Streptococcus hemolyticus*, *sulfadiazine* is the drug of choice. However, equally good results have been obtained with sulfanilamide or sulfathiazole. If these agents are used in adequate dosage, the therapeutic response is as dramatic as in the case of gonorrheal arthritis, as is illustrated in Case VI.

CASE VI.—Mr. J. P., a fifty-one-year-old, married Jewish printer, complained of chilly sensations followed by aches in arms and legs two weeks before admission to the hospital. Two days following the onset of illness, the left knee became suddenly swollen, red and painful. At first the swelling involved the entire knee but gradually localized in the prepatellar region.

Past history: Four years before admission to the hospital, the patient had had a somewhat similar episode, with sudden pain and swelling of the left knee lasting for ten days. The diagnosis made by his physician at that time was "gout."

The physical examination revealed no abnormality except for marked swelling and redness of the left knee with a small effusion in the joint itself and a very large amount of fluid in the prepatellar bursa.

The patient's temperature was 102° F.; the leukocyte count 17,000 cells per cu. mm., with 80 per cent of the cells polymorphonuclears. Urinalysis gave normal findings. There were 4.4 mg. of uric acid per 100 cc. of serum. Beta hemolytic streptococci were cultured from the synovial fluid.

The patient was given 6 gm. of sulfathiazole a day for five days and 2 gm. a day for seven days. The temperature fell slightly during the first forty-eight hours of sulfathiazole therapy and the pain, redness and heat in the knee were reduced slightly. The prepatellar bursa was excised because of the large amount of fluid it contained. Pain, swelling and tenderness of the knee improved, and patient was essentially symptom-free at the end of the twelve-day treatment period. The point of entry of the streptococcus was not determined.

Summary: After two weeks of persistent arthritis due to the beta hemolytic streptococcus this patient improved rapidly on adequate doses of sulfathiazole.

3. Staphylococcal Arthritis

The second most common form of pyogenic arthritis is that caused by the staphylococcus. Its entrance into the joints occurs under the same conditions as in the case of the *Streptococcus hemolyticus*. Sulfanilamide has little or no effect upon staphylococcal infections; however, recent developments indicate that sulfathiazole and sulfapyradine are of value in their treatment, as illustrated in the following case report.

CASE. VII.—Mr. R. K., a thirty-one-year-old, single Canadian cook, noted the sudden onset of a feeling of tightness in the right hand, followed by pain and tenderness in the wrist joint, ten days before admission to the hospital. During the twenty-four hours following the onset of pain, marked swelling, redness and warmth of the entire dorsum of right hand appeared and the patient had fever, malaise and anorexia. Two days before entry to the hospital, he had a shaking chill followed by high fever.

The patient gave a history of an attack of gonococcal urethritis with a residual stricture six years before entry to the hospital.

Physical examination revealed extreme swelling, redness and warmth of the entire dorsum of the right hand with acute tenderness over the right wrist and pain on flexion and extension of the fingers. The patient's temperature was 102° F., pulse rate 120. Leukocyte count was 11,000 cells per cu. mm., 69 per cent of the cells being polymorphonuclears. Cultures of prostatic secretion and of fluid from the right wrist joint were positive for *Staphylococcus aureus*. Sulfapyridine in doses of 4 to 6 gm. a day was given for thirty-nine days with resulting blood level up to 3.9 mg. per cent. Within twenty-four hours after the beginning of the treatment, the pain and swelling of the right hand began to subside. Thereafter, there was steady improvement and three weeks later the patient was symptom-free except for occasional slight aching and weakness and slight limitation of motion of the right wrist.

Summary: A case of acute arthritis due to Staphylococcus aureus, in which marked limitation of motion would have been expected, responded excellently to treatment with sulfapyridine.

4. Meningococcal Arthritis

Two forms of arthritis are associated with meningococcal meningitis and meningococcemia. The first occurs early in the course of the disease and affects multiple joints, often in symmetrical fashion. Pain and tenderness are present but no marked swelling or effusion. A hemorrhagic rash, attributed to hemorrhages in the articular or periarticular tissues, usually accompanies the preceding manifestations. The type of joint involvement just described presupposes unusually severe infection, but the joint symptoms are transitory and treatment of them is symptomatic.

The second form of meningococcal arthritis represents a metastatic pyarthrosis which usually occurs toward the end of the first week of illness. Ordinarily, only one joint is involved, most frequently the knee. In contrast to the first form, a large effusion and minimal to moderate signs of inflammation may be present. The diagnosis can be established by joint aspiration and demonstration of meningococci in the fluid aspirated. Our limited experience with the chemotherapy of purulent arthritis due to the meningococcus has given uniformly successful results. The drugs of choice are sulfadiazine and sulfanilamide. The results obtained in the treatment of a case of acute meningococcal meningitis and arthritis are illustrated in the following clinical abstract.

CASE VIII.—Mr. B. C., a twenty-year-old, married salesman, suddenly developed malaise, fever and stiff neck four days prior to his admission to the hospital. During the period of twelve hours following onset of symptoms, the patient had several shaking chills and noted generalized stiffness, aching and swelling of joints, most marked in the feet and hands. The fever and stiffness of his neck increased progressively and, on the third day before admission, he noted a rash resembling measles.

The past history was noncontributory.

On admission the patient was semicomatose. There were numerous small, purpuric spots over both hands and feet. The neck was extremely stiff. The left elbow was red, slightly swollen and warm. Temperature was 102° F., pulse rate 120. The white blood cell count was 14,400 per cu. mm., with 82 per cent of the cells polymorphonuclears. Lumbar puncture revealed a turbid fluid,

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Physical examination revealed extreme swelling, redness and warmth of the entire dorsum of the right hand with acute tenderness over the right wrist and pain on flexion and extension of the fingers. The patient's temperature was 102° F., pulse rate 120. Leukocyte count was 11,000 cells per cu. mm., 69 per cent of the cells being polymorphonuclears. Cultures of prostatic secretion and of fluid from the right wrist joint were positive for *Staphylococcus aureus*. Sulfapyridine in doses of 4 to 6 gm. a day was given for thirty-nine days with resulting blood level up to 3.9 mg. per cent. Within twenty-four hours after the beginning of the treatment, the pain and swelling of the right hand began to subside. Thereafter, there was steady improvement and three weeks later the patient was symptom-free except for occasional slight aching and weakness and slight limitation of motion of the right wrist.

Summary: A case of acute arthritis due to Staphylococcus aureus, in which marked limitation of motion would have been expected, responded excellently to treatment with sulfapyridine.

Past history: The patient had had three attacks of gonorrhea, the last attack fourteen years before admission. Treatment had never been adequate, and for the past ten years he had had occasional episodes of dysuria associated with urethral discharge.

The general physical examination on admission was negative. The left ankle was extremely red, swollen and tender with marked limitation of motion. Temperature was 102° F.; leukocyte count, 25,300 cells per cu. mm. Test for albumin in the urine gave a three plus reaction, and the urine was loaded with white blood cells. Cultures of urine and of fluid from the left ankle joint were positive for colon bacillus. Laboratory examination gave evidence of portal cirrhosis with a reversal of the albumin/globulin ratio, 15 to 20 per cent retention of brom-sulfalein and esophageal varices by x-ray.

The patient was given 7 gm. of sulfathiazole during the first twenty-four hours of treatment and then 4 gm. daily for four days. Within twenty-four hours there was a marked reduction in the pain in the ankle. Sulfathiazole was discontinued because of oliguria and hematuria and the appearance of many crystals in the urine. Urinary signs and symptoms increased during the following two weeks. Since it was felt that they were associated with the long-standing urinary infection, the patient was treated daily with 4 gm. of sulfadiazine for the following seven weeks. The ankle continued to improve slowly with the disappearance of the pain and swelling. However, limitation of dorsiflexion persisted and x-rays showed slight narrowing of the joint spaces with moderate decalcification of the bones. The urinary infection, on the other hand, did not respond. Urine cultures remained positive for colon bacillus and nonhemolytic streptococcus and the prostatic enlargement persisted.

Summary: In a patient with colon bacillus arthritis, urethritis and prostatitis the arthritis responded to treatment with sulfathiazole and sulfadiazine, but the urethritis and prostatitis persisted.

6. Pneumococcal Arthritis

Pneumococcal arthritis is a rare complication of pneumococcal pneumonia, occurring in approximately 0.1 per cent of the cases. Rarely, primary forms have been described also, as well as those accompanying other types of pneumococcal infection. The symptoms manifest are those of a septic joint.

which rapidly formed a pellicle. Initial pressure of the spinal fluid was 400 mm. of fluid. The fluid contained 3860 cells per cu. mm. and 372 mg. of protein per 100 cc. Smears and cultures of the fluid were positive for meningococci.

The patient was given 8 gm. of sulfadiazine a day for ten days. After twenty-four hours of treatment, his general condition improved markedly. Stiffness of neck and rash disappeared. However, fever, spiking daily to 103° F., persisted, as did slight swelling, tenderness and slight redness of the right wrist and right knee. Ten days after admission the right knee was aspirated and 40 cc. of turbid fluid, which clotted firmly, was obtained. The white cell count of the fluid was 7100 per cu. mm., 80 per cent of the cells being polymorphonuclears, and no organisms were grown on culture. The fever, joint pain and swelling subsided gradually. Three weeks after admission, the patient was essentially well.

Summary: In this case of acute meningococcal meningitis and arthritis the response to sulfadiazine treatment was slow but impressive.

5. Arthritis Due to the Colon Bacillus

Arthritis forms a rare complication of *Escherichia coli* infection. One or more joints may be involved and suppuration is the rule. The diagnosis is made by association with *E. coli* infection, usually of the genito-urinary tract, particularly of the prostate. The diagnosis can be corroborated by joint aspiration and demonstration of *E. coli* in the synovial fluid. As will be seen from the following case report, the treatment of patients suffering with arthritis caused by the colon bacillus with full doses of sulfathiazole or sulfadiazine can be extremely satisfactory.

CASE IX.—Mr. D., thirty-five years old, married, had had five attacks of pain and swelling of left hip, knee and ankle during the ten-year period prior to hospital admission. Each attack was of sudden onset and lasted several months. During the four years prior to hospitalization, he had been absolutely free from joint symptoms until eight days before admission when he had a severe shaking chill accompanied by a rise in temperature to 102.6° F. Two days later, he developed pain, redness and swelling of the left ankle.

Past history: The patient had had three attacks of gonorrhea, the last attack fourteen years before admission. Treatment had never been adequate, and for the past ten years he had had occasional episodes of dysuria associated with urethral discharge.

The general physical examination on admission was negative. The left ankle was extremely red, swollen and tender with marked limitation of motion. Temperature was 102° F.; leukocyte count, 25,300 cells per cu. mm. Test for albumin in the urine gave a three plus reaction, and the urine was loaded with white blood cells. Cultures of urine and of fluid from the left ankle joint were positive for colon bacillus. Laboratory examination gave evidence of portal cirrhosis with a reversal of the albumin/globulin ratio, 15 to 20 per cent retention of brom-sulfalein and esophageal varices by x-ray.

The patient was given 7 gm. of sulfathiazole during the first twenty-four hours of treatment and then 4 gm. daily for four days. Within twenty-four hours there was a marked reduction in the pain in the ankle. Sulfathiazole was discontinued because of oliguria and hematuria and the appearance of many crystals in the urine. Urinary signs and symptoms increased during the following two weeks. Since it was felt that they were associated with the long-standing urinary infection, the patient was treated daily with 4 gm. of sulfadiazine for the following seven weeks. The ankle continued to improve slowly with the disappearance of the pain and swelling. However, limitation of dorsiflexion persisted and x-rays showed slight narrowing of the joint spaces with moderate decalcification of the bones. The urinary infection, on the other hand, did not respond. Urine cultures remained positive for colon bacillus and nonhemolytic streptococcus and the prostatic enlargement persisted.

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The diagnosis must be confirmed by bacteriological examination of the aspirated synovial fluid. It is most important to distinguish the arthritis of serum sickness, in a patient to whom antipneumococcus serum has been given, from pneumococcal arthritis. The chemotherapeutic agent of choice in the treatment of this type of arthritis is sulfadiazine, although sulfathiazole can be employed.

TYPES OF SPECIFIC INFECTIOUS ARTHRITIS IN WHICH THE USE OF THE SULFONAMIDE COMPOUNDS IS OF QUESTIONABLE VALUE

1. Arthritis Associated with Undulant Fever

Symptoms referable to the skeleton are common during the acute and postfebrile periods of undulant fever, but cases of significant arthritis are rare. Occasionally, suppuration may be present, and then the process originates probably in the bone in the form of osteitis or osteomyelitis. Except by isolation of the brucella organism, there is no method by which the diagnosis can be proved. Skin and agglutination tests should be done in suspected cases. The results should be evaluated only in conjunction with the clinical findings. The earlier enthusiasm for the sulfonamides in the treatment of brucellosis has waned. A definite evaluation of their therapeutic efficacy cannot be established at this time.

2. Arthritis Associated with Lymphogranuloma Venereum

The course of arthritis associated with lymphogranuloma venereum has been variable, with chronic indolent forms showing a marked tendency to relapse more commonly than cases in which the joints are acutely inflamed. No evidence of bone or cartilage destruction has been seen in roentgenograms, and the synovial fluid has been nonpurulent. Although certain cases have persisted for six months or a year, spontaneous resolution takes place, as a rule, with no residual deformity or loss of function. For this reason, evaluation of therapy is difficult. Some success apparently has been obtained following the use of sulfanilamide. When employed, it should be administered in full doses.

TYPES OF ARTHRITIS ASSOCIATED WITH INFECTIOUS DISEASES IN WHICH THE USE OF THE SULFONAMIDE COMPOUNDS HAS NOT BEEN ESTABLISHED

1. Arthritis Associated with Scarlet Fever

The joint manifestations accompanying scarlet fever are commonly divided into three distinct forms: (1) an acute type of polyarthritis representing the onset or reactivation of rheumatic fever; (2) nonsuppurative arthritis with sterile joint effusion; (3) septic joints due to actual infection with the hemolytic streptococcus.

In the first form the clinical picture is that of rheumatic fever, except for an apparently lower incidence of endocarditis. The treatment is the same as for rheumatic fever. The second form usually occurs during the first two weeks of the disease and affects an average of three or four joints, often in a migratory fashion. Joint effusion, which is always sterile, may be present, and the arthritis is usually accompanied by fever. This manifestation of scarlet fever is uniformly self-limited with a duration of one or two weeks, but may recur. No specific measures are needed.

The suppurative form of arthritis following scarlet fever takes rank with other forms of sepsis due to the *Streptococcus hemolyticus* occurring in the second or third week of the disease. The symptoms and management are essentially those described under streptococcal arthritis, with emphasis being placed upon adequate dosage of sulfadiazine or sulfanilamide, to be given as soon as the diagnosis is made or suspected.

2. Arthritis Associated with Bacillary Dysentery

Arthritis is reported as occurring in about 3 per cent of the cases of bacillary dysentery. It may be associated with the acute attack of dysentery or appear at an interval up to four weeks. A few large joints are usually affected, and the condition is self-limited, rarely exceeding a duration of a few months. The mechanism of this form of arthritis is still obscure but probably represents a metastatic infection, since, in a few cases, the organism has actually been cultivated

from the joint. Treatment with sulfonamide compounds is probably without effect.

3. Typhoidal Arthritis

Arthritis forms a rare complication of typhoid fever. When this complication is present one or more joints may be involved and suppuration or ankylosis is unusual. The diagnosis is made by association with typhoid fever and the recovery of typhoid organisms from the joint. It is probable that most cases will eventually clear with immobilization and repeated aspirations. Sufficient data are not at hand to be able to draw any conclusions concerning the efficacy of the sulfonamide compounds in typhoidal arthritis.

4. Arthritis Associated with Subacute Bacterial Endocarditis

Joint pain and actual arthritis are occasionally encountered in association with subacute bacterial endocarditis. This is probably caused by the lodging of septic emboli in and around the joint. Inflammation of the joint usually disappears in a week or less. Suppuration never takes place and specific measures are rarely needed, but when they are, the choice of the sulfonamide compound should be governed by the causative agent.

5. Arthritis Associated with Chronic Idiopathic Ulcerative Colitis

The status of the arthritis that accompanies about 5 per cent of the cases of chronic ulcerative colitis of nonspecific origin still remains to be settled. In some cases the arthritis, in onset and in exacerbation, displays a temporal relationship to the course of the colitis; in other instances the two conditions behave entirely independently. Certainly the arthritis accompanying idiopathic ulcerative colitis differs clinically in no important way from rheumatoid arthritis, while pathological and bacteriological data, which might help to determine whether or not the two types are identical, are not yet available. Lacking further evidence, we see no reason to create a separate form of arthritis from the association with colitis. If the two conditions run a parallel course, with the colitis severe enough to call for consideration of surgical treatment,

the presence of arthritis constitutes a further argument for ileostomy and even colectomy. In these instances sulfonamide compounds may be helpful in preparing the patient for surgical treatment.

TYPES OF ARTHRITIS IN WHICH THE SULFONAMIDE COMPOUNDS HAVE PROVED INEFFECTUAL

1. Rheumatic Fever

The prophylactic value of sulfanilamide in rheumatic fever has been well established. Rheumatic exacerbations rarely occur when children are given prophylactic doses of sulfanilamide. The dose commonly employed is 2 to 3 gm. taken daily throughout the school year. Toxic symptoms appear in about 10 per cent of the children. Sulfanilamide is ineffective in the active treatment of rheumatic fever. When it is given during the active stage, or during convalescence from recent rheumatic attacks, recrudescences occur frequently.

2. Rheumatoid Arthritis

From our clinical results with sulfanilamide in the treatment of patients with rheumatoid arthritis, it seems fair to conclude that this form of therapy does not exert any specific effect on the agent causing the disease, nor does it influence the clinical course. The sedimentation rate is unaffected.

3. Tuberculous Arthritis

The sulfonamide compounds are ineffective in the treatment of tuberculous arthritis. Rest for both the local lesion and the patient is the keystone of good therapy.

4. Lupus Erythematosus Disseminatus

The articular lesions seen in lupus erythematosus disseminatus range from arthralgia or periarticular swelling, sometimes with effusion, to actual joint deformity. The use of the sulfonamide drugs is contraindicated, because it frequently results in accentuation or exacerbation of the disease process.

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LOW BACK PAIN AND THE LUMBOSACRAL JOINT*

LOUIS G. HOWARD, M.D., F.A.C.S.†

THE human body, in altering the function of its front extremities from weight-bearing legs to freely movable and highly specialized arms, and in changing the spine from a horizontal to an upright structure, has imposed the major portion of its weight upon the lumbosacral spine. This area of the spine is attempting to meet new demands upon it for increased stability; and here, as in other parts of the body which are passing through evolutionary stages, many anomalies of development are found. Some of these anomalies tend to strengthen greatly the area and meet the demands of increased stability; and some of the anomalies presented decrease the stability and predispose toward abnormally increased stress and strain which may result in disabling low back pain.

Recognition of the underlying factors of low back instability permits early proper treatment that may afford complete relief of symptoms and prevent the development of pathologic changes in articular cartilage, bone, intervertebral disks, ligaments and muscles, which may otherwise require prolonged and more radical and expensive treatment.

This discussion will be limited, for the most part, to a consideration of the anatomic variations frequently found in the lumbosacral spine and to a number of factors which tend to aggravate them, predisposing toward chronic low back pain. Also it will bring attention briefly to the importance of the intervertebral disk and rupture of the nucleus pulposus.

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SUMMARY

The advent of the sulfonamide compounds represents the greatest advance ever made in the treatment of joint disease. The dramatic alteration in the clinical course of many of the specific infectious arthritides, following the administration of sulfonamide compounds, is adequate evidence that they exert a specific chemotherapeutic effect on certain causative organisms. This effect is best demonstrated in gonococcal, streptococcal, staphylococcal, meningococcal, colon bacillus and pneumococcal infections. The sulfonamides are of questionable value in undulant fever and lymphogranuloma venereum. There are not sufficient data at hand to evaluate properly their efficacy in the arthritis associated with scarlet fever, bacillary dysentery, typhoid fever, subacute bacterial endocarditis and chronic idiopathic ulcerative colitis. They are ineffectual in rheumatic fever, rheumatoid arthritis, tuberculous arthritis and lupus erythematosus disseminatus; in fact, their use is contraindicated in rheumatic fever and lupus erythematosus disseminatus.

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IMPORTANT ANATOMIC VARIATIONS IN THE
LUMBOSACRAL SPINE

1. Lumbosacral angle and weight-bearing surface of sacrum:
 - (a) Near horizontal—stable weight-bearing plane (Fig. 178).
 - (b) Nearer vertical—unstable weight-bearing plane (Fig. 179).
2. Impingement of lumbar spinous processes (faceting and exostoses when lumbosacral angle is acute [Fig. 180]) from contact.
3. Plane of lateral articulation:
 - (a) Ideal: sagittal-parallel and internal-external—stable (Fig. 181).
 - (b) Unstable or hypermobile:
 - (1) Anteroposterior or oblique as in dorsal spine (Fig. 182).
 - (2) Cupped facets on top of sacrum (Fig. 183).
 - (3) Horizontal and small as in cervical spine (Fig. 184).
 - (4) Absent or very small lateral articulations.
4. Unfused first sacral segment. More vertical weight-bearing plane—unstable.
5. Sacralized transverse processes:
 - (a) Complete bilateral sacralization (Fig. 185).
 - (b) Complete unilateral sacralization (Fig. 186).
 - (c) Incomplete bilateral sacralization (Fig. 187).
 - (d) Incomplete unilateral sacralization (Fig. 188).
 - (e) Large transverse processes not sacralized (Fig. 189).
6. Weak posterior neural arch:
 - (a) Defective development of lamina, posteriorly (Fig. 190).
7. Weak lateral neural arch and spondylolisthesis:
 - (a) Pedicles.
 - (b) Laminae (isthmus between the superior and inferior lateral facets) (Fig. 191).
8. Posterior prominence of the fifth lumbar vertebra (Fig. 192).
9. Long lumbosacral spinous process (Fig. 193).
10. Hypertrophy of ligamentum flavum.
11. Pelvic tilt.
12. Damage to intervertebral disk (Fig. 194).

1. Lumbosacral Angle

(a) The lumbosacral angle, or angle between the sacrum and lumbar spine, has developed by elevation of the trunk and anterior extremities. It varies to a great degree all the way from an obtuse angle, where the superior surface of the sacrum is quite horizontal, to one wherein the angle may



Fig. 178—Stable weight-bearing plane of sacrum, near horizontal, with good lumbosacral angle.

approach 90 degrees and the top of the sacrum is nearly vertical. The obtuse lumbosacral angle presents a stable weight-bearing surface and the acute lumbosacral angle presents a varying degree of instability. (See Fig. 178.)

(b) With an acute lumbosacral angle, as the weight-bearing plane of the top of the sacrum approaches a vertical, the

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12. Damage to intervertebral disk (Fig. 194).

2. Impingement of Lumbar Spinous Processes

As the lumbosacral angle becomes more acute the spinous processes in that area approximate each other and often impinge. As a result of this impingement the contacting points become eburnated, dense, hard and faceted with reactionary exostosis formation, causing discomfort and a snapping sensation as they override each other (Fig. 180).



Fig. 180.—Impinging lumbar spinous processes caused by acute lumbosacral angle.

3. Planes of Lateral Articulations

(a) STABLE LATERAL ARTICULATIONS (Fig. 181).—What constitutes the ideal plane for lateral articulations between the fifth lumbar vertebra and the sacrum is a much disputed question among orthopedic surgeons who have given much thought, time and study to this subject, and there is no uni-

superimposed weight acts with much greater shearing stress and strain upon the lateral articulations, producing an arthrosis, and upon the ligaments which may be stretched abnormally (Fig. 179).

Some of the other factors producing an acute lumbosacral angle are poor posture, overweight, flexion contracture of



Fig. 179.—Unstable weight-bearing plane of sacrum, nearer vertical, with acute lumbosacral angle.

hips or knees, or both, and abnormal contractures of the fascia lata on one or both sides increasing pelvic obliquity.

If other bone anomalies are present in the lumbosacral area, they will be aggravated by an acute lumbosacral angle and generally their pathologic effect will be diminished as the angle becomes more obtuse and affords a better weight-bearing plane.

2. Impingement of Lumbar Spinous Processes

As the lumbosacral angle becomes more acute the spinous processes in that area approximate each other and often impinge. As a result of this impingement the contacting points become eburnated, dense, hard and faceted with reactionary exostosis formation, causing discomfort and a snapping sensation as they override each other (Fig. 180).

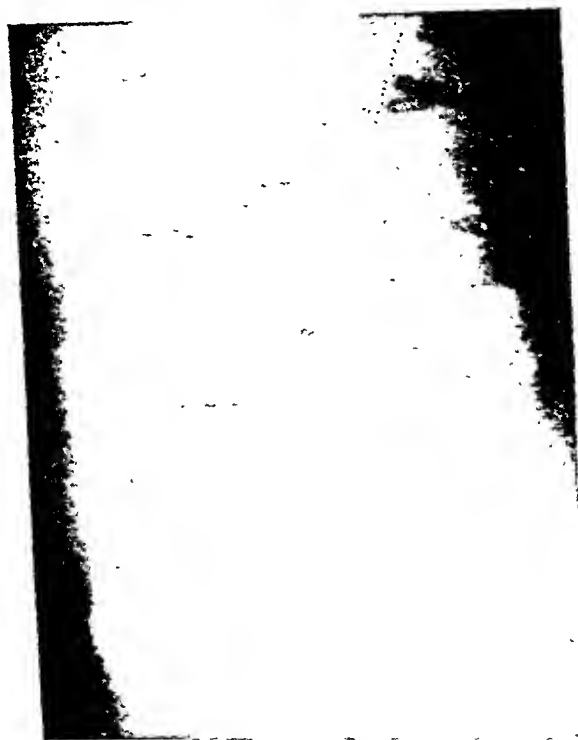


Fig. 180.—Impinging lumbar spinous processes caused by acute lumbosacral angle.

3. Planes of Lateral Articulations

(1) STABLE LATERAL ARTICULATIONS (Fig. 181).—What constitutes the ideal plane for lateral articulations between the fifth lumbar vertebra and the sacrum is a much disputed question among orthopedic surgeons who have given much thought, time and study to this subject, and there is no uni-

versal agreement. I believe, as a result of my own observation on several thousand spines, that the ideal plane is one which is vertical and internal-external and nearly in the sagittal plane. This produces relatively stable lateral articulations. At least, in my experience, individuals with lumbosacral spines having that type of lateral articulation and no anomalies have



Fig. 181.—Ideal planes of lateral articulations: sagittal and parallel, and internal-external—stable.

been singularly free from discomfort even though subjected to great strain because of occupation or sport. If the lumbosacral angle in these individuals becomes more acute, the shearing stress and strain may produce arthrosis sufficient to give symptoms, but this happens less often than with the unstable types of lateral articulations now about to be described.

(b) UNSTABLE LATERAL ARTICULATIONS.—There are many symmetrical and asymmetrical variations in the planes of the lateral articulations. The important consideration is whether or not a given type offers stability or instability plus hypermobility. In the case of asymmetrical lateral articulations, the question is whether or not the type on one side can work



Fig. 182.—Unstable planes of lateral articulations: anteroposterior or oblique as in dorsal spine.

freely and smoothly with the type on the other side. Often this is mechanically impossible. If instability or incompatibility, or both, exist, the basis for an arthrosis is present as a result of increased stress and strain, especially if the lumbosacral angle is quite acute. The arthrosis may be evidenced by eburnation of bone, thinning of articular cartilage, thickening

versal agreement. I believe, as a result of my own observation on several thousand spines, that the ideal plane is one which is vertical and internal-external and nearly in the sagittal plane. This produces relatively stable lateral articulations. At least, in my experience, individuals with lumbosacral spines having that type of lateral articulation and no anomalies have

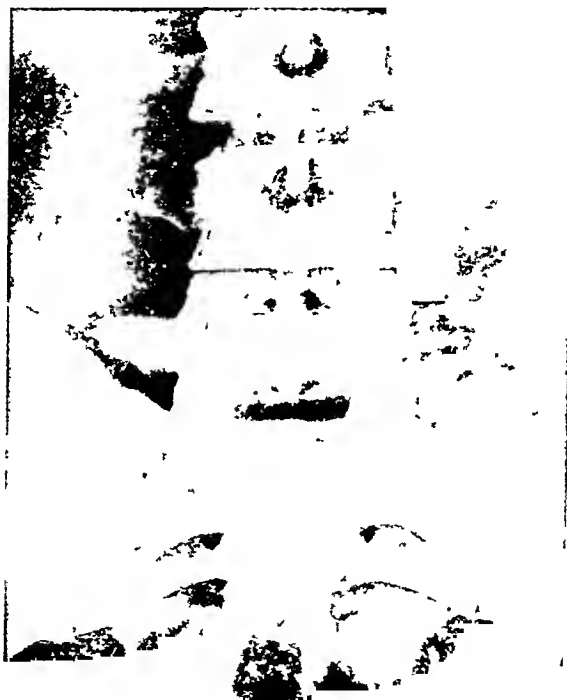


Fig 181—Ideal planes of lateral articulations sagittal and parallel, and internal-external—stable

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ever, generally there is some degree of asymmetry and that is the foundation of poor mechanics, which under unusual, sudden or repeated strains may initiate symptoms.

(2) *Cupped Facets on Top of Sacrum* (Fig. 183).—Often the anteroposterior lateral articulations, because of their hypermobility, form cup-shaped depressions in the posterior

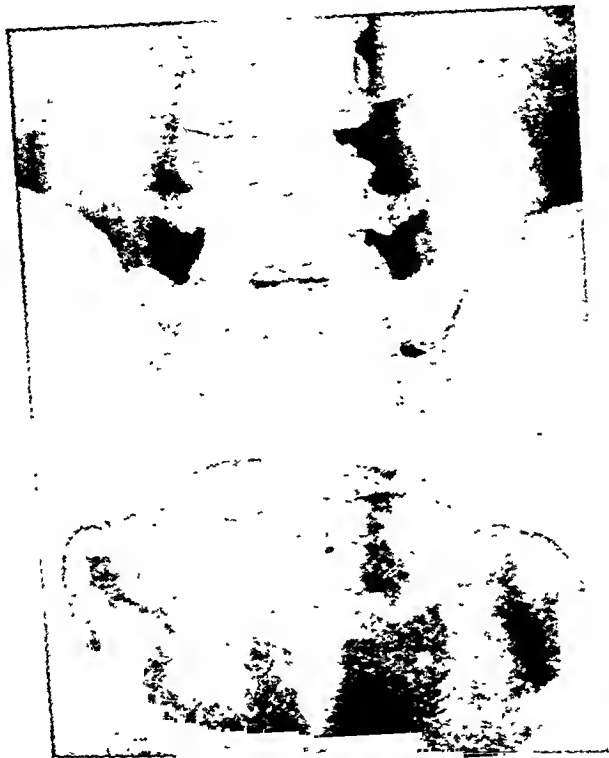


Fig. 184.—Unstable, hypermobile horizontal and small lateral articulations as in cervical spine.

part of the sacral articular facets permitting too great posterior displacement of the fifth lumbar inferior facet. This facet may catch in a serration or irregularity and result in very acute localized lumbosacral pain. (See heading 9.) The involuntary muscle spasm resulting from the excruciating pain locks the joint in this deforming position until released

of the joint capsule, inflammation of the synovial membrane, and proliferation of new bone about the periphery of the joint.

(1) *Anteroposterior Lateral Articulations* (Fig. 182).—This type often is symmetrical. It may be rather vertical and somewhat at right angles to the internal-external type. It is



Fig. 183.—Unstable, hypermobile lateral articulations with cupped facets on top of sacrum.

so common that some authorities consider it normal although the writer does not for the reasons previously given in the discussion of stable lateral articulations. This type has much greater anteroposterior motion than the internal-external type. If symmetrical, this anomaly may give no symptoms even though it may have a fairly acute lumbosacral angle. How-

sometimes develop into trick heavy lifters and obtain positions on the stage or in the circus.

(b) COMPLETE UNILATERAL SACRALIZATION (Fig. 186).—Occasionally a spine is found with the fifth lumbar transverse process of one side enlarged and united by a solid bony fusion



Fig. 185.—Complete bilateral sacralization of lumbar transverse processes—stable.

to the sacrum. The opposite transverse process may be of normal size or enlarged but not in contact with the sacrum. This anomaly offers increased stability but often gives pain because associated with the various types of sacralization we find bizarre varieties of very unstable rudimentary lateral articulations.

by a change in position, sometimes obtainable only by manipulation under anesthesia.

(3) *Horizontal or Cervical Type of Lateral Articulation* (Fig. 184).—A very bad type of lateral articulation is the small oblique or horizontal type similar to that normally found in the cervical spine. It is too small and too unstable to function properly as a weight-bearing joint in the lumbosacral spine, and is very easily strained.

(4) *Absent or Very Small Lateral Articulations*.—Occasionally a lumbosacral lateral articulation is exceedingly small or absent. This condition makes for great instability. It is found in a large percentage of the cases to be described under "Sacralized Transverse Processes."

4. Unfused First Sacral Segment

Rarely there is a failure of fusion of the first to the second sacral segment. Since this failure of fusion really makes the first sacral a part of the lumbar group, we should consider that it brings the effective weight-bearing plane from the top of the first sacral to the top of the second sacral segment, which generally is nearer a vertical plane and therefore diminishes stability. This is a retrogressive stage in evolution because it increases the number of lumbar vertebrae.

5. Sacralized Transverse Processes

A progressive evolutionary condition is the diminution of the number of lumbar vertebrae. This is important, and is accomplished by fusion of enlarged fifth lumbar transverse processes to the wings of the sacrum and occasionally by a fusion of the vertebral body itself to the sacrum.

(a) *COMPLETE BILATERAL SACRALIZATION OF FIFTH LUMBAR* (Fig. 185).—Sometimes the fifth lumbar transverse processes are very large and extend downward to form a bony fusion with the wings of the sacrum. If the vertebral body also is fused to the sacrum, the result is greatly increased stability because the effective weight-bearing plane then is the top of the fifth lumbar vertebrae, which generally is more nearly horizontal than the usual weight-bearing plane. Persons with such a fusion of lumbar vertebrae and sacrum

transverse process contacts one flattened wing of the sacrum by an accessory joint. One extra joint is to be considered and it may show arthritis. Very often the lateral articulations are rudimentary and unstable.

(e) **LARGE TRANSVERSE PROCESSES NOT SACRALIZED** (Fig. 189).—Often the transverse processes are quite large and ir-

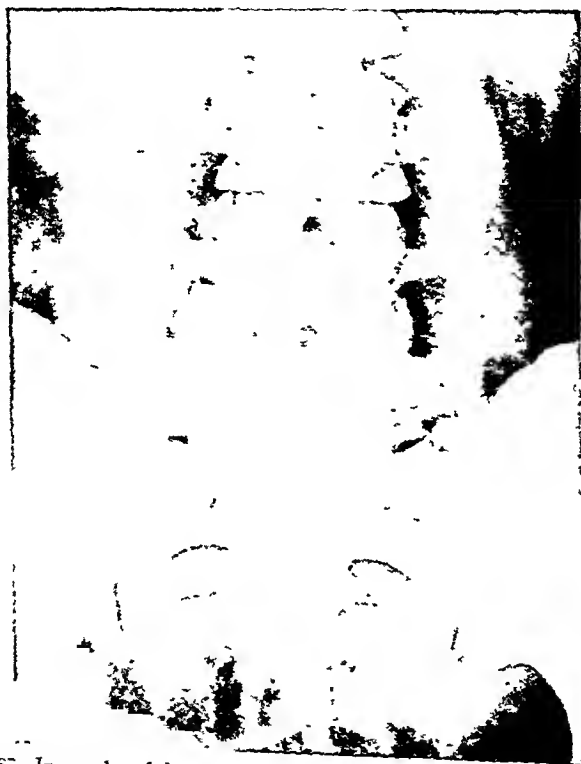


Fig. 187.—Incomplete bilateral sacralization of lumbar transverse processes with two extra sacral joints and arthritis in one.

regular in shape but do not form a joint with the sacrum. If there is a question about contact with the ilium, x-rays taken at a 45-degree angle in the anteroposterior plane will show whether there is a space or contact. If contact with the ilium is present, there may be some pain associated with the anomaly.

(c) **INCOMPLETE BILATERAL SACRALIZATION** (Fig. 187).—Incomplete bilateral sacralization is characterized by enlarged fifth lumbar transverse processes which make contact with the flattened wings of the sacrum by means of an accessory joint on each side. The joints may be small or large and may vary in size on each side. In general they make for increased



Fig. 186—Complete unilateral sacralization of a lumbar transverse process

stability but add two joints that may present some degree of arthritis. Again it is quite likely that rudimentary lateral articulations between fifth lumbar and first sacral will be found and these may contribute to the disabling instability.

(d) **INCOMPLETE UNILATERAL SACRALIZATION** (Fig. 188).—In incomplete unilateral sacralization only one enlarged

transverse process contacts one flattened wing of the sacrum by an accessory joint. One extra joint is to be considered and it may show arthritis. Very often the lateral articulations are rudimentary and unstable.

(e) **LARGE TRANSVERSE PROCESSES NOT SACRALIZED** (Fig. 189).—Often the transverse processes are quite large and ir-



Fig. 187.—Incomplete bilateral sacralization of lumbar transverse processes with two extra sacral joints and arthritis in one.

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6. Weak Posterior Neural Arch

Frequently one finds various degrees of failure of development of the neural arch posteriorly (Fig. 190), generally where the spinous process should be, or an open defect on either side of it. Sometimes the whole back portion of the

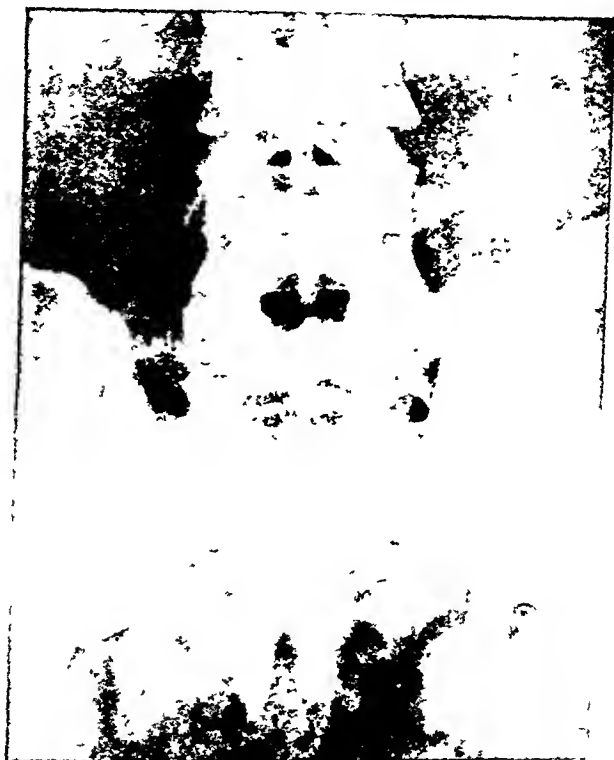


Fig. 188.—Incomplete unilateral sacralization of a lumbar transverse process and with one extra joint.

neural arch is deficient. When these defects are large they rarely cause pain; when narrow or irregular they may cause some discomfort, if a portion of the cauda is bound down by adhesions to the membranes, and if the membranes are caught in a fold of the *ligamentum flavum*. This latter condition is extremely infrequent, but has been observed.

7. Weak Lateral Neural Arch and Spondylolisthesis

Weakness or failure of development of the lateral portion of the neural arch is found most often in one of two areas: (a) the pedicles on one or both sides rarely, and (b) the isthmus of the lamina between the superior and inferior lateral articular facets on one or both sides commonly. Either

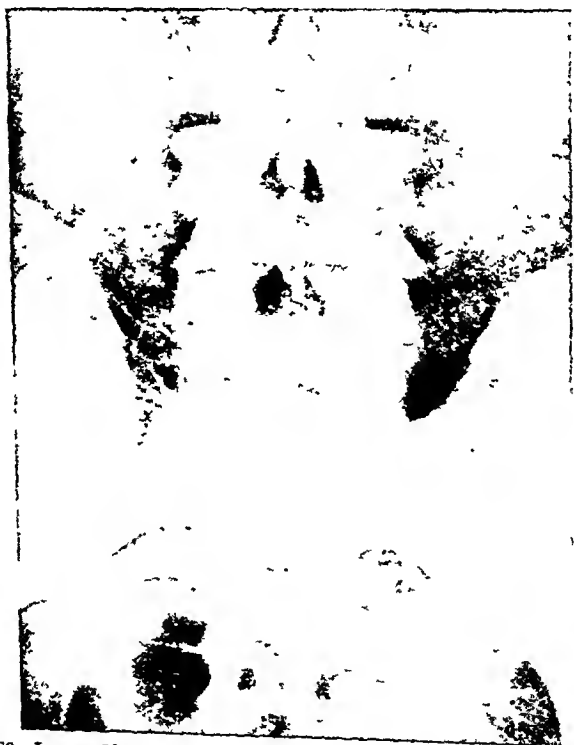


Fig. 189.—Large fifth lumbar transverse processes not sacralized. No extra joints. Unstable lateral articulations.

condition when unilateral makes for instability on the side where it occurs and throws abnormally greater stress and strain upon the opposite side and may cause pain. But when either condition is bilateral, the vertebral body and vertebrae above have a tendency to slide forward upon the surface of the sacrum or vertebra below. This condition is called "spon-

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S-shaped surface on the sacrum or inferior vertebra as shown in the lateral x-ray.

An important medicolegal question is the consideration of whether or not spondylolisthesis is the result of a fracture of the pedicles, or the isthmi of a lamina, or the result of weakness due to faulty development. A determining factor in mak-



Fig. 191.—Weak lateral neural arch and spondylolisthesis. Defect of laminae between superior and inferior lateral facets.

ing a decision is the condition of the apposing surfaces of the vertebrae or vertebra and sacrum. If these surfaces are molded and thus exhibit changes which could occur only after a long period of instability, obviously the spondylolisthesis could not have resulted from a recent fracture; but if these same surfaces are flat the defect could be the result of a

dylolisthesis." It is a common cause of discomfort because of the stretching of ligaments and pressure upon the cauda equina. (See Fig. 191.)

The gradually widening defect may fill in with scar tissue, and sometimes this scar tissue may calcify and attain sufficient strength to prevent further forward displacement of the

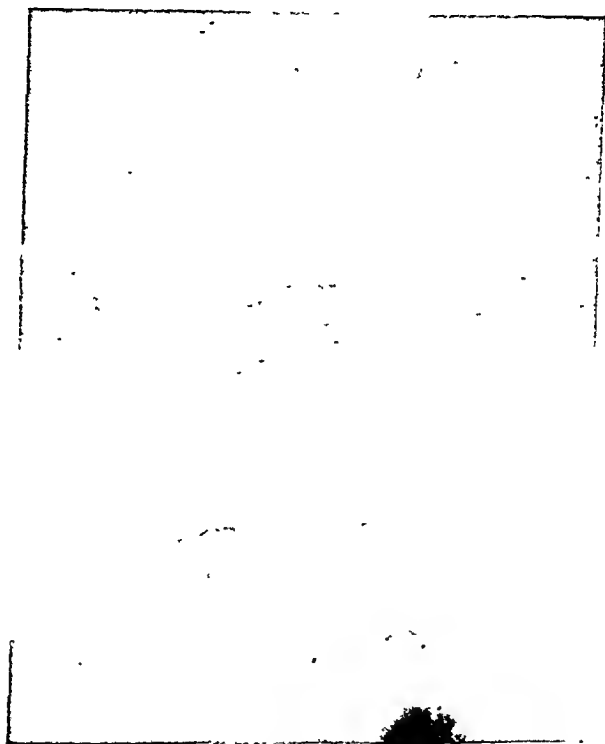


Fig. 190.—Weak posterior neural arch. Defective development of laminae posteriorly.

vertebral body. More often this gap increases and the vertebra slides forward and backward upon the sacrum or inferior vertebra to such an extent that the intervertebral disk is worn out and the inferior surface of the affected vertebral body becomes cup-shaped posteriorly, by molding itself over the top of the sacrum or inferior vertebra, and forms an

stretch the capsule of the affected lateral articulations. The resulting pain causes extreme involuntary muscle spasm that locks the articular facets in this abnormal relationship, which, at times, may be corrected only by manipulation of the lumbosacral spine, the patient being well anesthetized, or cured by a spine fusion.



Fig. 193.—Long lumbosacral spinous process making pressure upon cauda equina through defect in upper sacral neural arches.

9. Long Lumbosacral Spinous Process

Rarely, as a result of congenital fusions to the spinous process of the first, and possibly also to the second and third sacral spinous processes, the fifth lumbar spinous process is very long. Associated with this peculiar anomaly there is a posterior defect in the sacral neural arch so that, if the lumbo-

recent fracture. Spondylolisthesis from fractures is very rare and seldom occurs, but is a possibility.

8. Posterior Prominence of the Fifth Lumbar Vertebra

Posterior displacement of the fifth lumbar vertebra (Fig. 192) is the result of hypermobility of the lateral articulations



Fig. 192.—Posterior prominence of fifth lumbar vertebra in relation to sacrum.

plus stretching of the joint capsule and supporting ligaments. Often it is maintained by serrations or irregularity in the posterior portion of the sacral facet. It may also be found between other vertebrae. Some orthopedists doubt the existence of such an entity, but it is a very real one to the sufferer and excruciating pain may result from motions which further

stretch the capsule of the affected lateral articulations. The resulting pain causes extreme involuntary muscle spasm that locks the articular facets in this abnormal relationship, which, at times, may be corrected only by manipulation of the lumbosacral spine, the patient being well anesthetized, or cured by a spine fusion.



Fig 10:—Long lumbosacral spinous process making pressure upon cauda equina through defect in upper sacral neural arches

9. Long Lumbosacral Spinous Process

Rarely, as a result of congenital fusions to the spinous process of the first, and possibly also to the second and third sacral spinous processes, the fifth lumbar spinous process is very long. Associated with this peculiar anomaly there is a posterior defect in the sacral neural arch so that, if the lumbo-

sacral angle is acute, this abnormally long process may dip into the defect and cause pressure upon the cauda equina (Fig. 193). Also on lateral motion it may impinge against the opposite side of the defect in the sacrum.

10. Hypertrophy of the Ligamentum Flavum

Sometimes the ligamentum flavum is greatly thickened and hypertrophied, especially in very unstable lumbosacral spines. This thickening or hypertrophy may cause discomfort by pressure upon the cauda equina. The ligamentum flavum has been found three to six times its normal thickness in some unstable lumbosacral spines.

11. Pelvic Tilt

Any abnormal permanent tilt of the pelvis may produce pathologic changes in the lateral articulations with resultant mechanical arthrosis and pain. Lateral tilt of the pelvis is more often caused by contractures from muscle imbalance, unilateral leg shortening, and also by hip or knee flexion deformities. Forward tilt of the pelvis may be due to faulty development, tight fascia lata, and to poor posture. In general, correction of the pelvic tilt will help reduce discomfort from an unstable lumbosacral spine.

Pelvic obliquity due to abnormally tight fascia lata may often be corrected by exercises to stretch the fascia, but frequently it may have to be divided surgically as advocated by Ober. In properly selected cases relief from symptoms by surgery is startlingly rapid and complete.

12. Damage to Intervertebral Disk

The intervertebral disk may become fractured by sudden or repeated trauma, with rupture of the nucleus pulposus and extrusion of a small or large portion of the disk posteriorly to press upon the cauda equina, causing symptoms very much like those produced by unstable lumbosacral spines (Fig. 194). In about one half of such cases the total protein content of the spinal fluid may be elevated. In many cases one may have to depend upon detailed x-ray studies with oxygen or lipiodol in the spinal canal for a definite diagnosis. Abnormal

deviation of the column of oxygen or lipiodol within the canal may clinch this diagnosis. Often the diagnosis can be made with the aid of a careful history and neurological examination but the abnormal displacement of oxygen or lipiodol shows the size, shape and exact location of this protruding mass.



Fig. 194.—Damage to intervertebral disk and protrusion of nucleus pulposus into spinal canal causing almost complete block of column of lipiodol.

If lipiodol is employed, it should be removed, after suitable roentgenograms have been obtained, to prevent the possibility of later inflammation within the spinal canal.

Associated with protrusion of ruptured nucleus pulposus there is generally intractable sciatica with or without long remissions from direct pressure upon the cauda equina. Due

to muscle spasm the lumbosacral curve may be obliterated. There may or may not be loss of ankle jerk on the affected side, but if it is diminished or lost it helps point to cauda equina pressure. When present, the areas of numbness in the leg and foot help to indicate the level of the protrusion within the spinal canal.

DIFFERENTIAL DIAGNOSIS

Tumors of the Cauda Equina

Tumors of the cauda equina may cause symptoms identical to those produced by an unstable lumbosacral spine or by a disk protruding in that area. Roentgen studies and careful neurological examination frequently will differentiate the cause of the discomfort.

Visceral Disease

Pathologic changes in the abdominal viscera (such as ulcer, carcinoma, or retrocecal appendix), diseases of the pelvic organs (such as tumor of the ovary or uterus, retroversion of the uterus, and disease of the prostate) and diseases of the retroperitoneal area (such as infections in or about the kidney, or stone in the urinary tract) may all refer pains to the back. Therefore, much attention should be given to examination of the abdomen and pelvis.

To draw a conclusion about the cause of low back pain before making a detailed, careful, complete physical examination, which includes the abdomen and pelvis, may be disastrous for the patient. One should never forget that visceral disease may refer pain to the back and that to neglect such disease and treat the lumbosacral instability not only may do no good, but might prolong suffering that proper study and treatment could easily and quickly relieve.

Diseases of the Spine and Pelvis

Diseases of the vertebrae and bones of the pelvis may cause severe backache but will not be discussed here owing to limitation of space. However, they should always be considered and a careful search should always be made for them and appropriate treatment given when indicated.

Sacro-iliac Strain

Sacro-iliac joints possess a variable degree of mobility. They are large joints and generally are quite stable. However, some are sufficiently hypermobile to permit a slight displace-

TABULATION

DIFFERENTIAL DIAGNOSIS BETWEEN LUMBOSACRAL AND SACRO-ILIAC PAIN

Examination	Sacro-iliac Pain	Lumbosacral Pain
Local pain on pressure.	Increased.	Increased.
Stand: Bend forward.	Lumbar spine bends but guardedly.	Lumbar spine splinted; bends little or none.
Stand: Bend backward.	May bend freely but often guardedly.	Generally very little backward bending.
Stand: Lateral motion.	May bend freely.	Often about half normal lateral motion.
Stand: Rotation.	May rotate but little due to pain and spasm.	Generally fair rotation.
Stand: Bend forward, then elevate trunk.	Generally limited forward motion and generally extends fairly well.	Generally limited forward bending and often more pain when extending than when flexing and with catching sensation in lumbosacral spine.
Walk up steps.	Pain on affected side. Avoids weight on affected side with limp.	May aggravate pain.
Sitting: Sit and bend forward.	Avoids weight on affected side. Less pain than when standing and bending.	May have no lumbosacral motion due to aggravation and muscle spasm.
Lying: Back down (a) Acute thigh and knee flexion, and rotation of adducted thigh.	Aggravates pain.	May aggravate pain after lumbosacral motion begins.
(b) Straight leg raising (Lasèque).	Sciatic nerve stretches throughout.	
(1) 0°-20° (2) 20°-70° (3) 70°-90° causes lumbosacral motion and severe torque upon sacro-iliac joint.	May have aggravation. Aggravated by torque upon sacro-iliac. Aggravates pain because of torque upon sacro-iliac.	No aggravation. Not aggravated until flexion causes lumbosacral motion. Aggravates pain because it produces lumbosacral motion.
Lying: Prone (a) Flex knee.	Aggravates pain.	May have aggravation of pain.
(b) Leg hyperextended with knee flexed.	May aggravate pain.	May have aggravation of pain.
(c) Raise legs to hyperextended spine.	May aggravate pain.	Generally aggravates pain.

ment when subjected to abnormal stresses or strains. This displacement may cause great pain and that pain is usually located directly about the sacro-iliac joint and is seldom re-

to muscle spasm the lumbosacral curve may be obliterated. There may or may not be loss of ankle jerk on the affected side, but if it is diminished or lost it helps point to cauda equina pressure. When present, the areas of numbness in the leg and foot help to indicate the level of the protrusion within the spinal canal.

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Tumors of the cauda equina may cause symptoms identical to those produced by an unstable lumbosacral spine or by a disk protruding in that area. Roentgen studies and careful neurological examination frequently will differentiate the cause of the discomfort.

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Diseases of the vertebrae and bones of the pelvis may cause severe backache but will not be discussed here owing to limitation of space. However, they should always be considered and a careful search should always be made for them and appropriate treatment given when indicated.

really limit lumbosacral motion and protect that area from strain. Most corsets and belts on the market fail to give adequate support to the low back, with disappointing results.

A well fitting *plaster jacket* gives excellent support, but any back causing symptoms severe enough to warrant a jacket needs other treatment first.

Posture education and instruction in the proper manner to reach down for objects and lift without strain are very important.

Exercises are helpful to correct the lumbosacral angle and strengthen abdominal and back muscles so that a patient may discard his brace and depend upon his own musculature for adequate support.

Local heat followed by proper massage over the back and legs is soothing and gives great relief from symptoms of discomfort.

The more acutely painful cases may often be greatly relieved by gentle, firm *manipulation* under anesthesia. These manipulations should not be done until after a definite diagnosis has been determined and proved by x-ray. The manipulation consists of moving the lumbosacral spine throughout its complete normal range of motion with all involuntary muscle spasm eliminated by the anesthesia. Special attention to the exact planes of the articular facets as shown by the x-ray determines the arcs of motion to be employed in the manipulation and those that should be avoided. Usually manipulation should be done with the patient under anesthesia, because then only light force is necessary and involuntary protective muscle spasm is not present to interfere with or complicate the procedure.

Surgical Treatment

In chronic cases of low back pain presenting gross anatomical variation or with definite arthrosis (as described in headings 1 to 8 inclusive) surgery may often be an immediate choice; and to delay the surgery in many of these cases is to prolong the suffering or insure further recurrence of symptoms.

Because of the great tendency in some insurance and in-

ferred as in lumbosacral anomalies or disease. Most painful sacro-iliac joints also show a variable degree of arthritis, and it is the arthritic condition which is aggravated by the strain that causes the discomfort.

Some sacro-iliac joints possess accessory articular surfaces varying in size. These are rare. When such sacro-iliac joints are painful, x-ray plates generally show some arthritic change in these accessory articular surfaces.

Most strains of the sacro-iliac joint are rotary in nature.

An outline of the differential characteristics of lumbosacral and sacro-iliac pain is given in the tabulation on page 1573.

Roentgenologic Examination of the Lumbosacral Spine

In addition to a careful history and physical examination, detailed roentgenograms are essential. The reader is referred especially to the publications of Dr. A. B. Ferguson,^{1, 2} also to his great classified collection of roentgenograms of lumbosacral anomalies demonstrated in the Lame Back Exhibit of the recent Annual Meetings of the American Medical Association.^{1, 2, 3}

TREATMENT OF LOW BACK PAIN DUE TO LUMBOSACRAL INSTABILITY

Conservative Treatment

Conservative treatment for low back pain due to lumbosacral instability consists mainly of all those factors which rest the back.

Bed rest is important, especially on a bed made reasonably even and firm by placing under the mattress a board of $\frac{1}{4}$ -inch, three- or five-ply veneer cut a little smaller than the mattress.

Efficient *adhesive strapping*, tightly applied across the whole lumbosacral spine both transversely and diagonally to extend down toward the greater trochanters and a bit forward of a line from the greater trochanter upward toward the axilla to a level of about the first lumbar vertebra, often gives considerable relief in acute back strain.

A well fitting *brace* may be applied when the patient is up and about. This brace should be so constructed that it will

really limit lumbosacral motion and protect that area from strain. Most corsets and belts on the market fail to give adequate support to the low back, with disappointing results.

A well fitting *plaster jacket* gives excellent support, but any back causing symptoms severe enough to warrant a jacket needs other treatment first.

Posture education and instruction in the proper manner to reach down for objects and lift without strain are very important.

Exercises are helpful to correct the lumbosacral angle and strengthen abdominal and back muscles so that a patient may discard his brace and depend upon his own musculature for adequate support.

Local heat followed by proper massage over the back and legs is soothing and gives great relief from symptoms of discomfort.

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Surgical Treatment

In chronic cases of low back pain presenting gross anatomical variation or with definite arthrosis (as described in headings 1 to 8 inclusive) surgery may often be an immediate choice; and to delay the surgery in many of these cases is to prolong the suffering or insure further recurrence of symptoms.

Because of the great tendency in some insurance and in-

dustrial accident cases toward magnification of symptoms, the greatest care should be employed in the selection of those cases for surgery. Only patients who are reasonably cooperative and cannot respond to conservative treatment should have a spine fusion.

Technic of the Spine Fusion of Hibbs.—The one operation that gives greatest permanent relief is a Hibbs' spine fusion, which obliterates all further motion in the affected area. The technic is rather poorly described in most orthopedic textbooks; therefore, the author feels constrained to repeat here the technic as taught to him by the late Dr. Russell Hibbs and his associates.

Through a midline posterior incision the spinous processes of the upper sacral segments and lower lumbar vertebrae are exposed by a subperiosteal dissection that is then extended laterally out over the laminae to include the lateral articular facets, from which the cartilage is thoroughly and completely removed with thin osteotome and curet. The interspinous ligament is entirely excised and all but a thin layer of the ligamentum flavum is removed. The edges of the laminae are completely denuded of ligament. The cortex is then removed with a sharp chisel from the back of the laminae and upper posterior surface of the sacrum over a rather wide area down to bleeding bone; the removed bone fragments are so turned or placed, with their cancellous side down over the back of the sacrum and interlaminar spaces, as to stimulate rapid interlaminar fusion. The spinous processes are cut off at the base, split longitudinally, and these fragments also are overlaid upon the interlaminar bridges to further strengthen them. A sliver of bone is forced into every one of the denuded lateral articulations to hasten fusion there. Whenever a lumbosacral spine is particularly unstable ten or twelve additional grafts about $1\frac{1}{4}$ by $\frac{1}{4}$ by $\frac{1}{4}$ inch are removed from the posterior superior border of the ilium and packed upon the fusion area to overlap each other and thus furnish a large amount of available bone and calcium to form a very massive fusion.

The extent of the fusion for the unstable lumbosacral spine is determined by x-ray and should extend upward from the

sacrum to include the unstable vertebrae. Generally it is sufficient to fuse only from the fourth lumbar to the first sacral but often from the fifth lumbar to the first sacral is enough. However, occasionally one must fuse from the third lumbar to the first sacral.

Postoperative Care.—Following the operation the patient may have complete horizontal bed rest for a period ranging from one to three months depending upon the type of instability for which the operation was performed. During this time a back brace is generally worn. Just before permitting the patient to get up the author applies a well fitting, long plaster jacket which the patient wears until x-rays show a good, solid fusion. The jacket is then replaced by the brace that the patient wore in bed and this is worn for a variable period of from two to four months more, on the average, or until such time as the x-ray may show massive, dense, continuous, bony fusion throughout the operative area. During all of this time exercises are given to strengthen supporting muscles. After removal of the brace, exercises are given to restore normal mobility to the area not treated surgically.

The spondylolisthesis patients need the longest postoperative bed rest and use of a jacket and brace. Bed rest may last eight to ten weeks and may be followed by wearing a jacket for eight to twelve more weeks. The total period of support depends upon the degree of spondylolisthesis and the density and cross sections of the fusion mass. Following a firm solid fusion with restoration of painless motion in the area not operated upon, restriction is gradually removed.

For the great majority of all cases properly selected for operation the patients make a complete recovery.

Treatment of Conditions not Covered Under Previous Discussion

If it gives discomfort, the rare *abnormally long lumbosacral spinous process* (described in heading 9) may be excised completely with its enveloping periosteum. If the periosteum should not be removed, a new spinous process will form. Relief brought about by removal of this anomaly is often spectacular. The operation is simple.

The degree of *hypertrophy of the ligamentum flavum* (de-

scribed in heading 10) seems to occur in relation to the amount of lumbosacral instability; therefore, it is found generally when one is fusing a lumbosacral spine and, because removal of the ligament is part of the spine fusion operation, it is difficult to evaluate the relief afforded by excision of the ligament alone. The author has not limited himself to that operation in any case.

Abnormal pelvic obliquity caused by unilateral or bilateral tightening of the fascia lata (described in heading 11) may often be corrected by posture education plus special exercises to stretch the fascia, thus reducing the amount of pathologic stress and strain upon the lumbosacral spine. If the fascia cannot be stretched by a sufficient amount by exercises, it may be divided transversely, as advocated by Ober, resulting in enough relief to make spine fusion unnecessary in a number of cases.

A ruptured intervertebral disk causing intractable low back pain and sciatica (as described in heading 12) should be excised. Whether or not spine fusion should follow is determined by the degree of lumbosacral instability and the amount of bone structure removed in order to excise the tissue pressing upon the cauda equina.

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TREATMENT OF POLIOMYELITIS*

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THE treatment of poliomyelitis has passed through many phases of fads and fancies. In no other epidemic disease during the past thirty years has there been such divergence of concepts as to its nature, and such violent disagreement as to how the patient should be cared for. At first the disease was regarded as a neurologic problem and extensive neurological examinations were made and various forms of electrotherapy were used to stimulate the involved nerves and muscles. The disease was then passed on to the orthopedist who stressed the importance of early immobilization, but soon varied his procedures to include the use of hot packs, massage and various forms of physiotherapy. There was a short digression when the immunologists attacked the disease and introduced first the use of convalescent serum and then preventive vaccination, both of which were found to be of no practical value. Urotropin, suprarenalin, ephedrine, potassium chlorate, the sulfonamides and the vitamins have all been used with such contradictory results as to imply that their value is questionable, to say the least.

The adequate treatment of the acute stage of poliomyelitis

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requires the cooperation of the physician, orthopedist, physiotherapist and experienced nurse, and should include the utilization of all measures which are consistent with our knowledge of the disease. The character of this disease is such that an outbreak tends to create panic in the community and often results in unsound regulations. For instance, in one village situated on a main highway an ambulance carrying a patient with respiratory paralysis to a hospital was stopped at the outskirts and forced to make a wide detour. Other examples of unsound medical procedures precipitated by a sense of fear or by the pressure of inexperienced lay opinion could be cited, but suffice it to say that it is up to the individual physician to keep the public from becoming panic-stricken and from demanding improper restrictions.

PROBLEMS OF THE GENERAL PHYSICIAN

A practical method of approaching the treatment of acute poliomyelitis is to submit some of the pertinent questions most frequently asked by the graduate students in this clinic. The answers presented here merely represent certain aspects of our present knowledge, and are not to be construed as final. Much of the management of poliomyelitis is based on pure empiricism rather than on scientific fact, so that our methods and procedures are constantly subject to change. With these cautioning words let us examine the problem of acute poliomyelitis as it is faced by the general physician.

1. What Is the Nature and Etiology of Poliomyelitis?

Acute anterior poliomyelitis is at present considered to be a communicable disease whose etiologic agent is an extremely small filtrable virus. The virus is resistant to 1 per cent phenol and 15 per cent ether and apparently to the usual degree of chlorination used to destroy enteric bacteria in drinking water. It is destroyed by oxidizing agents such as hydrogen peroxide and potassium permanganate, by ultraviolet rays, and by heating to 55° C. or higher for five minutes.^{1,2} It is necessary here to say a word about the claim that the etiologic agent is a pleomorphic streptococcus. In our opinion, this is a very speculative hypothesis, for the great bulk of evi-

dence supports the virus theory, and as yet there is no proof that any bacteria can metamorphose into a virus state. Furthermore, the use of Rosenow's serum, which is derived from the so-called pleomorphic streptococcus, has been conclusively shown to be of no curative value in human poliomyelitis.³

2. How Is the Disease Transmitted and How Does the Virus Invade the Human Body?

Poliomyelitis is believed to be transmitted by contact either with an active case or with a healthy carrier. The virus has been isolated from the secretions of the nasopharynx² of infected cases and from the stools of both patients and healthy carriers. Sabin¹ found the virus in the feces of 40 per cent of adult cases and in 64 per cent of cases in children under eight years of age. This implies a higher degree of infectiousness of cases in children as compared to adult cases, a situation known to exist in uncomplicated scarlet fever convalescence. It is of interest that Sabin and Ward were unable to recover the virus from the oral secretions, the urine, or the nasal secretions. It seems to be generally agreed that the virus is not found in the blood or spinal fluid.⁴ The fact that the virus appears to be excreted mainly in the feces, with the nasal secretions as a possibility, suggests a communicability through contact and possible spread in the manner of enteric diseases, and explains its prevalence in summer. It is, therefore, essential to isolate any active case, and all soiled linens must be sterilized and the feces properly disposed of. In the home the linens should be soaked in boiling water with soap, and the stools can be disinfected with chloride of lime as in typhoid fever. It is possible that insects, such as flies, may play a role in the spread of the disease by the contamination of food, and, therefore, patients should be carefully screened. The virus gains entry to man either via the nasopharynx or the gastro-intestinal tract. Since the virus is neuronotropic and can multiply only in the neurons of susceptible hosts, it gains access to the central nervous system possibly by traveling along the olfactory nerve, or probably along the unmyelinated fibers of the thoracolumbar portion of the au-

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has discussed the diagnostic difficulties in connection with lymphocytic choriomeningitis. If the diagnosis is clearly established by obvious paralyses and the meningeal symptoms are not severe or are subsiding, a lumbar puncture is not warranted, and recently Paul⁶ has warned against unnecessary trauma to the patient in the early stages. However, a lumbar puncture for diagnostic purposes carefully performed should in no way disturb the choroid plexus, and in cases of elevated pressure slow drainage can be a therapeutic procedure.

6. How Should the Nonparalytic Form Be Managed?

In this type the virus either has not reached the cord or has not produced sufficient nerve damage to produce paralyses. The treatment is symptomatic and supportive. Analgesics, sedatives and even opiates may be necessary to keep the patient comfortable. Muscle pain and skin hypersensitivity are usually relieved by the application of hot packs for twenty minutes to one hour, several times a day. It must be stressed that patients must be individualized, and some are best left alone. The hot packs do not alter any impending pathologic changes in the cord but often relieve pain by counteracting the muscle spasm present early in the disease. It is of the utmost importance that nonparalytic cases should be examined monthly for a year for signs of weakness, especially in the back muscles.

7. How Should a Case with Paralyses or Muscle Weakness Be Managed?

There is no way of altering the pathologic processes in the central nervous system by the virus, nor can paralyses be prevented by any medical procedures. The use of convalescent serum which was so prevalent a decade ago is of no value after paralyses have developed, and carefully controlled studies have shown that its use in the preparalytic stage does not prevent paralyses.^{3,7} Therefore, the treatment here, too, is symptomatic and supportive. The patient should lie on a flat bed or in the neutral rest position, as will be described under physiotherapy. A board is placed at the foot of the bed, separated from the mattress by blocks. This open space

tonomic nervous system, presumably being taken up in the pharynx or small intestine.

3. Is It Necessary to Hospitalize Every Patient with Poliomyelitis?

The need for proper isolation and the dangers of complications requiring specialized treatments and care by well trained personnel make hospitalization desirable. In our opinion the dangers of a long trip to a hospital in a good ambulance are outweighed by the advantages gained after reaching a properly equipped hospital. At the Haynes Memorial Hospital we receive cases of acute poliomyelitis and any cases in which the diagnosis may be suspected. These patients are strictly isolated in a separate portion of the hospital, and scrupulous care is taken to prevent upper respiratory infections from reaching them. Medical aseptic care is observed throughout, and relatives are allowed to see the patients only from the doorway of the ward. Treatment of each case is individualized, and, as is absolutely essential, the medical, orthopedic and physiotherapy staffs cooperate early and throughout the course of the disease.

4. Is It Necessary to Isolate Contacts?

The state and local Boards of Health control the regulations governing contacts. Every physician is duty bound to cooperate with these departments in every way. The social service problem of poliomyelitis should begin with the sympathetic but firm reasoning of the family physician at the time the diagnosis of poliomyelitis is made. Any contact who is not feeling well should be carefully studied for early symptoms.

5. When Should a Lumbar Puncture Be Performed?

Lumbar puncture is of distinct diagnostic value. Early in the abortive forms it may present negative findings, but later it is a valuable adjunct in establishing a diagnosis. It is important to remember that the spinal fluid findings alone will not rule out a lymphocytic choriomeningitis or a mumps encephalitis, and that in all cases the history of exposure and the clinical symptoms must be carefully considered. Lucchesi²

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physical condition and living on the best of diets succumb to this disease.

10. When Should the Respirator Be Used?

A patient should be placed in the respirator when respiratory difficulty is due to intercostal or diaphragmatic paralysis. This is usually associated with or preceded by weakness of the neck and shoulder muscles.¹¹ It is necessary to ascertain whether the patient can use his diaphragm or his intercostal muscles. Inability to count slowly without constantly taking a breath is a good test. If diaphragmatic or intercostal weakness is suspected, the patient should immediately be sent to a hospital properly equipped with a respirator. Delay in cases of this type is dangerous. Respiratory difficulty due to bulbar paralysis is not aided by the respirator, but it must be remembered that bulbar and spinal paralyses can coexist. Hiccup is a serious prognostic sign and is a contraindication for the respirator. Bulbar paralysis often is accompanied by pharyngeal paralysis and difficulty in swallowing necessitating the use of the suction apparatus and tube feeding.

11. Does Tonsillectomy Predispose to Poliomyelitis?

Statistics show that recent tonsillectomy predisposes to poliomyelitis and particularly to the bulbar form. Since tonsillectomy is usually an elective operation as to time, it would seem advisable not to have it performed during the summer months, especially during an outbreak of poliomyelitis.^{12, 13}

12. What Is the Present Status of the Kenny Treatment?

Sister Kenny, a nurse from Australia, has captured the attention of the medical profession by showing up the sins of commission and omission in orthodox poliomyelitis treatment. Like all Calvinistic reformers, she is sure of her ground, insists on an elaborate ritual from her followers, and, according to one investigating committee, seems to have misused the term "cure."¹⁴ It is questionable whether this reform could have been brought about in a conciliatory tone because the errors were as deep-rooted as were bleeding, blistering and

prevents the heels from resting on the mattress, and when the patient is turned permits the toes to hang straight downward with the feet firmly against the footboard as they are when the patient is on the back. The patient is preferably turned by the nurse, but little children are often difficult to control in this respect. Hot packs are applied wherever there is pain or where spasm is elicited. The frequency of the hot packs is governed by the severity of the discomfort of the patient. Analgesics in the form of aspirin and codeine may be used if the hot packs fail to relieve. As the tenderness and pain subside, education of muscle groups is cautiously begun by the physiotherapist. Later, when the acute stage is past, active exercises are instituted and such residual paralyses as exist become the problem of the orthopedist.

8. Are There Any Safe Prophylactic Measures Against Poliomyelitis?

Active immunization against poliomyelitis has been abandoned because in order to be effective a live virus must be used, and this has proved to be too dangerous. The use of zinc sulfate instillations for temporary protection has likewise been abandoned because it has been found to be ineffective. This procedure has three distinct disadvantages, namely, the pain involved, the trauma to the nasal mucosa, and the possibility of producing loss of the sense of smell for a long period.⁸

9. Are Any of the Newer Drugs or Vitamins of Value in the Treatment of Poliomyelitis?

Chemotherapy through the use of sulfonamides has been of no value in animal experimentation. It has been reported on favorably in human poliomyelitis,⁹ but the conclusions drawn as to its value are so vulnerable that they do not inspire confidence. Deficiencies in vitamins B₁, C and D have all been incriminated, but the evidence at hand suggests that such deficiencies are of no great importance.⁸ Indeed, malnutrition or the lack of vitamins appears to play no significant role in susceptibility to poliomyelitis.¹⁰ Every summer we are struck by the fact that so many persons in apparently perfect

physical condition and living on the best of diets succumb to this disease.

10. When Should the Respirator Be Used?

A patient should be placed in the respirator when respiratory difficulty is due to intercostal or diaphragmatic paralysis. This is usually associated with or preceded by weakness of the neck and shoulder muscles.¹¹ It is necessary to ascertain whether the patient can use his diaphragm or his intercostal muscles. Inability to count slowly without constantly taking a breath is a good test. If diaphragmatic or intercostal weakness is suspected, the patient should immediately be sent to a hospital properly equipped with a respirator. Delay in cases of this type is dangerous. Respiratory difficulty due to bulbar paralysis is not aided by the respirator, but it must be remembered that bulbar and spinal paralyses can coexist. Hiccup is a serious prognostic sign and is a contraindication for the respirator. Bulbar paralysis often is accompanied by pharyngeal paralysis and difficulty in swallowing necessitating the use of the suction apparatus and tube feeding.

11. Does Tonsillectomy Predispose to Poliomyelitis?

Statistics show that recent tonsillectomy predisposes to poliomyelitis and particularly to the bulbar form. Since tonsillectomy is usually an elective operation as to time, it would seem advisable not to have it performed during the summer months, especially during an outbreak of poliomyelitis.^{12, 13}

12. What Is the Present Status of the Kenny Treatment?

Sister Kenny, a nurse from Australia, has captured the attention of the medical profession by showing up the sins of commission and omission in orthodox poliomyelitis treatment. Like all Calvinistic reformers, she is sure of her ground, insists on an elaborate ritual from her followers, and, according to one investigating committee, seems to have misused the term "cure."¹⁴ It is questionable whether this reform could have been brought about in a conciliatory tone because the errors were as deep-rooted as were bleeding, blistering and

purging at the beginning of the last century. Her denunciation of the sins of immobilization may go too far, but her recognition of the importance of muscle spasm in a plan of treatment and her method of overcoming it form a distinct contribution to medicine. Much of what she advocated has been practiced for many years in a modified form by a few clinicians, but to Sister Kenny belongs the credit of having held the torch of reform aloft. The greatest danger today is in accepting her theories and her methods as final.

We have too long been stressing the damage to the anterior horn cells as the sole cause of "paralysis" in the acute stage, when, as a matter of fact, much of the apparent paralysis is the result of spasm in opposing muscles supplied with healthy nerve fibers. We now focus attention on the side effects of this cord damage, and strive to prevent unnecessary loss of function of those muscle fibers that are in spasm. The gist of the Kenny treatment consists in hot packs to relieve muscle spasm, and with the relief of spasm the institution of measures designed to avoid mental alienation of muscle and incoordination of muscle function. The hot packs are wrung twice through a tight wringer and applied as often as is necessary. For further details one is referred to the articles of Pohl¹⁵ and Daly et al.¹⁶

Sister Kenny's attitude and that of her strict followers in completely condemning the respirator is to be deplored. The respirator is an instrument requiring judgment and skill. Properly used it saves lives by avoiding impending anoxemia as dramatically as intubation in laryngeal diphtheria. In fact, a fatigued patient will often promptly go to sleep when placed in the respirator. Sleep supplies the nearest approach to relaxation in this highly complex process. It is necessary to bear in mind that no less than 120 muscles take part in dyspneic breathing. Those engaged in expiration succumb most rapidly to fatigue and cannot be reached by hot packs. One could and should apply hot packs to the chest to relax spasm in inspiratory muscles, but not at the expense of delay in getting the patient to a respirator.

In the past immobilization has been too often dangerously prolonged and reeducation of muscles has been instituted too

late. The early medical care today should embrace early physiotherapy to avoid muscle spasm if we are to minimize the number and extent of deformities that need strictly orthopedic care. In view of the present trend it is highly probable that the neurologist may again take the lead in guiding us in many of the perplexing problems presented by the acute stage of poliomyelitis.

PHYSIOTHERAPY AND ORTHOPEDIC TREATMENT

Hot packs are used in the earliest stages to combat pain and tenderness. The frequency of the applications is adapted to the needs in each case, care being taken not to fatigue the patient. This part of the treatment is best managed by the experienced head nurse, and really comes under nursing care.

Today the physiotherapist sees the patient early in the disease. We no longer wait for muscle tenderness to subside, for it is during this period that so much can be done to gain the patient's confidence, to allay his fears, and to introduce him to our method of treatment. A detailed muscle examination is not made at this time because we believe that strong contractions of the muscles may cause damage. Furthermore, we consider it often inadvisable for the patient to be fully aware of the extent of his paralysis until the time arrives to overcome muscle incoordination.

We are at present in the throes of a revolution regarding the treatment of the affected muscles. Much misunderstanding has resulted from the interpretation of what actually has happened to these muscles. Some are in spasm as a direct result of neuron damage. Others are in sympathetic spasm through synaptic influences. Indeed, the whole process may be largely due to chemical changes within the synapses of the anterior horns, with relatively little cell destruction. This newer conception places the emphasis on muscle education and supports the Kenny technic which is designed to bring control of the mind over intact nerve channels and to overcome errors resulting from incoordination. The Kenny technic, by doing away with immobilization, by relaxing spasm and by the early education of muscles, tends to avoid deformities. It does not pretend to overcome actual paralyses

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Paralysis of Muscles of Back, Abdomen and Extremities

Symptoms	Treatment
Spasm in muscles opposed to paralyzed muscles.	Neutral rest position.
Incoordination of muscle groups.	Hot packs. Frequency of application according to severity. Cover such parts as are involved.
Muscle tremors and tenderness.	Baking continued until pain and tenderness have subsided.
Pain in any part of affected muscles.	Analgesics if heat fails to relieve.
Hypersensitive areas of skin.	Catheterization when necessary.
Backache. Headache.	Gentle passive motion of all joints three times a day. Range of motion determined by toleration.
Fever.	Gentle massage.
Sweating and flushing of skin.	Temporary splints for badly damaged muscle groups. (Remove for bath and massage.)
Apprehension. Resigned, quiet state.	Education of muscle groups.
Mental alienation.	Active exercises.
Tendency to gradual stiffening of paralyzed muscles.	Orthopedic measures. ^{17, 18}
Residual paralysis.	

from anterior horn cell destruction. It remains to be seen whether Sister Kenny's condemnation of exercises under water is justified on the grounds that they are apt to encourage incoordinated movements. There are brilliant successes and tragic failures under all the different highly developed physiotherapeutic technics. We confess that our own physiotherapy is undergoing such radical changes that we hesitate to go into details which may be revised next week.

Before starting treatments of affected muscles, an individual *muscle test* is made and charted as follows:

- Gone—No contraction seen or felt.
- Trace—Tightens but does not move part.
- Poor—Muscle moves part with gravity.
- Fair—Muscle moves part against gravity.
- Good—Muscle moves part against gravity and some resistance.
- Normal.

Outlines of Daily Physiotherapy

1. HEAT. Hot packs early. Later radiant heat—hood bakers—from ten minutes to one-half hour.
2. MASSAGE. Gentle massage of the entire body. The amount depends entirely on the condition of the patient. As the muscle strength increases, longer and slightly heavier massage may be given.

OUTLINE OF TREATMENT OF ACUTE POLIOMYELITIS

NONPARALYTIC FORM

Symptoms

Treatment

(The age of the patient modifies all treatment)

MILD

Rigidity of neck and spine.
Fever.
Backache, headache.
Sometimes vomiting or diarrhea.

Bed rest.
Bowels kept regular without undue purgation.
Fluids, soft solids.
(Lumbar puncture for diagnosis)

SEVERE

Increased rigidity of neck and spine.
Spasms of the back muscles.
Muscle tremors.
Soreness in other parts.
Hypersensitive areas of skin.
Sweating, especially about the head.
Restlessness.

Bed rest on flat bed in neutral rest position of the entire body.
Hot packs to back and to any painful parts.
Lumbar puncture for diagnosis.
If pressure is high, lumbar drainage.
Monthly examinations for weakness.

PARALYTIC FORM

CRANIAL, BULBAR

Ocular.
Facial.
Palatal. Nasal twang to voice. Regurgitation of liquids through the nose.
Pharyngeal. Gurgling of mucus in throat due to respiratory obstruction, from difficulty or inability to swallow.
Respiratory center involved. Respiration irregular, jerky and ineffective.
(Neck drop when patient is lifted by shoulders and deltoid weakness apt to accompany this type.)
Apprehension. Restlessness.
Ineffective cough.

Ocular, facial and palatal paralyses tend to recover spontaneously.
Severe palatal may necessitate tube feeding.
Suction (aspiration). Avoid injury to mucous membrane.
Feeding by tube passed through nose to stomach.
Respiration will not synchronize with respirator, which is therefore contra-indicated.

SPINAL

Respiratory

Weakness or paralysis of rib-raising muscles. (Accentuation of diaphragmatic breathing.)
Weakness or paralysis of diaphragm: Unilateral or bilateral.
Partial or complete.
(Accentuation of activity of rib-raising muscles.)
Neck drop and deltoid weakness.
Inability to cough.
Apprehension. Restlessness.

Respirator. Delay in placing patient in respirator tires out the weakened muscles and hastens paralysis, besides inducing anoxemia.
Weaning of patient from respirator is a very variable process and should always be done as soon as possible; it can be hastened by use of hot packs to chest.

Combination of Spinal and Bulbar Forms of Respiratory Paralysis

Respirator may be tried cautiously.

Paralysis of Muscles of Back, Abdomen and Extremities

Symptoms

Treatment

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Outlines of Daily Physiotherapy

1. HEAT. Hot packs early. Later radiant heat—hood bakers—from ten minutes to one-half hour.
2. MASSAGE. *Gentle* massage of the entire body. The amount depends entirely on the condition of the patient. As the muscle strength increases, longer and *slightly* heavier massage may be given.

3. **EXERCISE AND MUSCLE TRAINING.**—*Active Exercises.*—Active exercises are graded according to the amount of power in the muscles:

- (1) Gravity eliminated and with assistance.
- (2) Gravity eliminated without assistance.
- (3) Against gravity with assistance.
- (4) Against gravity without assistance.
- (5) Against gravity and assistance.

Every exercise should be a voluntary one. The patient must concentrate on the movement as the operator helps him to perform it. Exercises are all given in a slow rhythmical manner, allowing ample time after each contraction for complete relaxation of that muscle group. We do not confine our exercises to the affected muscles, as the unaffected muscles should be put through their normal range of motion.

Starting with three only of each exercise, we gradually increase the number as the patient improves until we reach a maximum of ten for each exercise. We have found that with the baking and massage this is sufficient. A complete rest follows every treatment.

SURGICAL TREATMENT OF POLIOMYELITIS

1. Braces and appliances.

These are not used until such time as it is possible to make some prognosis as to the amount of recovery of muscles to be expected. Use of braces may be considered under the following headings:

- (a) To assist recovery of weak muscles by preventing undue stretching.
- (b) To stabilize joints when this improves function.
- (c) To prevent and correct deformities.

2. Correction of deformities by stretching methods:

- (a) Manual, repeated.
- (b) Braces.
- (c) Plaster applications, repeated.
- (d) Skeletal traction by wires.

3. Tenotomies, tenodesis, fasciotomies.

4. Muscle transplants:

- (a) To improve muscle balance.

- (b) To supplement weakened muscles and improve function.
5. Osteotomies. To correct rotation deformities and restore alignment.
 6. Arthrodesis for stabilization purposes.
 7. Remodeling operations such as astraglectomy and bone blocks.
 8. Leg equalizing operations:
 - (a) Leg lengthening.
 - (b) Arresting growth.
 - (c) Leg shortening.
 9. Improvement of circulation, such as lumbar sympathectomy.

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PRINCIPLES OF REFRACTION*

HARRY K. MESSENGER, Ph.D., M.D.†

INTRODUCTION

To understand rightly the nature and significance of the refractive errors of the eye and the methods employed for their measurements and correction, requires an elementary knowledge of certain optical principles. These simple principles, if properly grasped at the outset, will be found to lighten rather than increase the strain of learning.

Rays

Let it be supposed that somewhere in space is a luminous point. Rays of light proceed from this point in all directions, unless intercepted. These rays do not exist as such, but have a very useful conceptual value: each ray serves to indicate that light is proceeding in a particular direction, even though light itself is not propagated in the form of rays. Books can be and have been written on the nature of light and its propagation. But by using the ray as the symbol expressing the very common perceptual experience, namely, that light travels in straight lines in an optically homogeneous transparent medium, we are availing ourselves of a simple and expressive scientific shorthand.

Object and Image Points. Focus

Our luminous point in space, from which rays are diverging and proceeding in all directions, unless intercepted, will be seen only if one or more of these rays enters the eye; and will be seen as a point only if the divergent rays that enter the eye are rendered convergent by the optical system of the eye and brought again to a single point upon the retina.

* From the Department of Ophthalmology, Harvard Medical School and the Massachusetts Eye and Ear Infirmary.

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This single point upon the retina is called the *image point*, and corresponds to the luminous source or *object point*. Light diverges from the object point, as we have seen, and converges to form the image point. Obviously, if the object point is to be seen clearly as a point, the *focus* of the convergent rays must be upon the retina; that is, the point to which the rays are converging must be upon the retina and not in front of or behind it. *Focus* is another symbol of which we shall make frequent use: by it we mean the point (or sometimes a line) to which rays converge or from which they diverge.

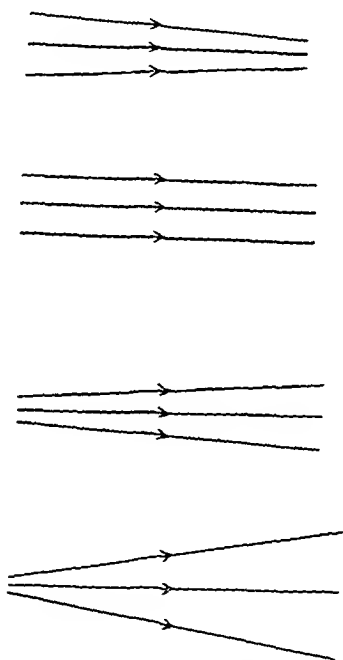


Fig. 195.—Convergent, parallel and divergent rays or lines. The convergent rays, if prolonged, would meet at a point. The two sets of divergent rays would in each case meet at a point if prolonged backward.

Vergence of Rays

Let us consider four groups of rays or lines (Fig. 195). The lines of the first group are convergent; of the second, parallel; of the third, divergent; of the fourth, also divergent,

but more divergent than those of the third. The lines of the second group, being parallel, that is, neither convergent nor divergent, are said to have zero vergence. By the general term *vergence* we denote both convergence and divergence. Since divergence is a dispersive function, it may appropriately be referred to as *minus vergence*, and likewise convergence may be spoken of as *plus vergence*.

The Measurement of Vergence

The third and fourth groups of lines have minus vergence, that is, are divergent, but they are unequally so. Let us now see how the vergence of straight lines (or rays) may be measured and expressed numerically.

FOCAL DISTANCE.—For the present we are speaking of straight lines that diverge from, or converge to, a point. With one exception, as we shall see later, we are concerned in refraction only with lines that diverge from, or converge to, a point. Even parallel lines, which have been said to have a vergence of zero, are conceived as divergent from, or convergent to, a point. This point, however, is situated at an infinitely remote distance, or, as is said, at infinity. If somehow we relate vergence to the distance of the focal point, that is, the point from which lines diverge, or to which they converge, and which for convenience we may call the *focus*, we have a ready means of expressing vergence numerically. The more remote the focus, the less the vergence. This is the same as saying that the vergence varies inversely as the *focal distance*, that is, the distance from the focus. Such an inverse variation may be expressed in terms of a fraction, the numerator of which is unity, and the denominator of which is the focal distance. If $V =$ vergence, and $F =$ focal distance, then $V = \frac{1}{F}$.

THE DIOPTR.—In optics, as in all branches of science, the metric system is (or should be) used exclusively. If $F =$ 1 meter, which is taken as the unit of focal distance, then V itself $= \frac{1}{1}$ or unity. The unit of vergence is the *dioptr*. When lines converge to a focus one meter away they are

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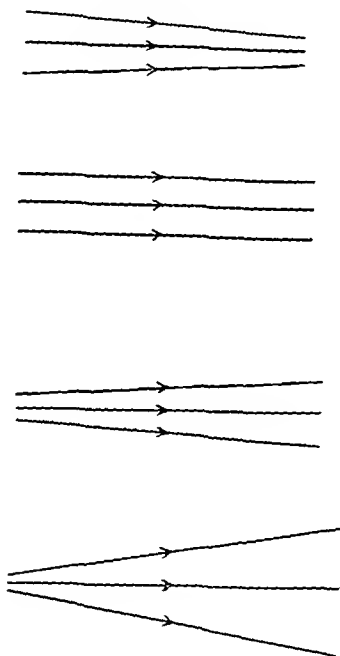


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dioptric value increases. In plane E it is $+8D$ (that is, $V = \frac{1}{F} = \frac{1}{\frac{1}{8}\text{m.}} = 8D$). In plane F, where the rays are at the focal plane itself, that is, at zero distance from it, the dioptric value of the light is infinity ($V = \frac{1}{F} = \frac{1}{0\text{m.}} = \infty D$). The further the light is from its focus, the less is its dioptric value. Thus, in plane A the dioptric value is only $+1.50D$ (that is, $V = \frac{1}{F} = \frac{1}{2\text{m.}} = .50D$). At an infinite distance from the focus the rays satisfy the definition of parallel lines, and their dioptric value is zero (that is, $V = \frac{1}{F} = \frac{1}{\infty\text{m.}} = \text{zero } D$). With similar calculations the dioptric value of divergent rays of light may be determined, only that in this case the values are always minus.

The Dioptric Power of a Lens

It was said above that light travels in a straight line in an optically homogeneous transparent medium. But if there is a change of optical density, as occurs when light traveling in

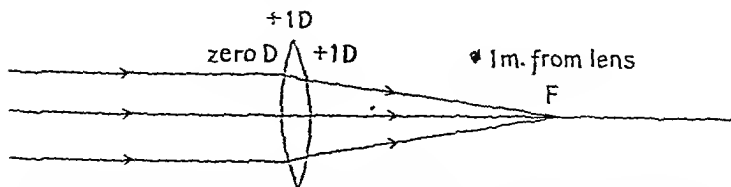


Fig. 197.—Refraction of light by a convergent lens, with a real image at F of an object point situated at an infinite distance in front of the lens.

air strikes the surface of a lens, the dioptric value of the light will suddenly change at the surface of the lens. Another such change in dioptric value will occur at the second surface as the light emerges. Since a change in dioptric value is effected at each surface of a lens, it may be said that the individual surfaces, or the lens as a whole, have *dioptric power*.

Let us take the case of parallel rays of light incident upon a lens (Fig. 197). Being parallel they have a dioptric value of zero at any plane along their course. Hence the dioptric value of the light incident upon the lens is zero. But these

said to have a vergence of plus one diopter ($+1D$). Thus the vergence of rays of light may be expressed in terms of the reciprocal of the focal distance expressed in meters.

The Dioptric Value of Light

Let us consider a pencil of light rays or lines converging to a point F (Fig. 196), at which point they all meet and from which they then continue divergent. The pencil of light has naturally three dimensions, though in the diagram only two are shown. Along the path of the pencil let us mark various planes at right angles to the chief ray of the pencil, and let

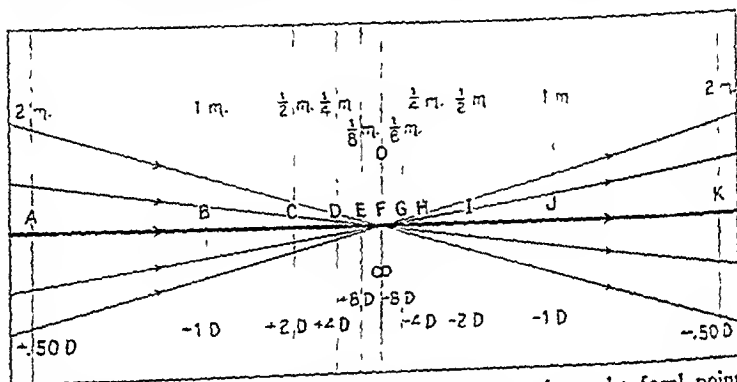


Fig. 196.—The dioptric value of light. Distances from the focal point F are expressed in meters. The corresponding dioptric values of the light for each distance are given below.

these planes be at the distance indicated from the focal plane, which passes through F . The rays passing through the plane at B are converging to a point in a plane one meter away; hence their vergence as they pass through plane B is said to be $+1D$ (that is, $V = \frac{1}{F} = \frac{1}{1m.} = 1D$). Or, we may say that these rays as they pass through plane B have a *dioptric value* of $+1$. But these selfsame rays, when they have proceeded further on their course and have reached plane C , are now convergent to a point only $\frac{1}{2}$ meter away. Their dioptric value, therefore, in plane C is $+2D$ (that is, $V = \frac{1}{F} = \frac{1}{\frac{1}{2}m.} = 2D$). As the rays approach plane F their

the lens the image will be found. Such an image is *real*, being actually formed by the meeting of convergent rays of light.

A VIRTUAL IMAGE.—But not all images are real. Suppose an object point is situated at a distance of $\frac{1}{2}$ meter from a $\div 3D$ lens (Fig. 199). In this case the dioptric value of the incident rays is $-4D$, since they are diverging from a point $\frac{1}{2}$ meter in front of the lens. The dioptric value of the emergent light is $-1D$ ($-4D \div 3D = -1D$). The emergent rays, being still divergent, will never meet. Their dioptric value being $-1D$, they diverge as if from a point 1 meter in front of the lens, at which point the image is said to be. But in this case the image, being an "as if" affair, is said to be *virtual*. A real image can be formed only by convergent rays of light actually meeting.

The Forms of an Ophthalmic Lens

When we say that a lens has a dioptric power of $\div 1D$, we really mean that the sum of the dioptric power of the indi-

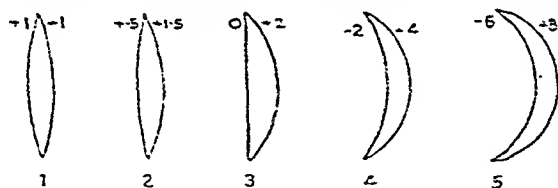


Fig. 200.—The forms of lenses. A $\div 2D$ sphere made up in five different forms.

vidual surfaces equals $\div 1D$. Strictly speaking, the thickness of the lens would also have to be allowed for in determining the dioptric power of the lens as a whole, but for all practical purposes of exposition the thickness of an ophthalmic lens may be considered as having only a negligible effect upon its dioptric power. By distributing the power in various ways over the two surfaces an infinite variety of *forms* for a lens of any given power can be designed. Thus in Fig. 200 the lenses of different forms all have a dioptric power of $\div 2D$. The sum of each pair of surfaces is $\div 2D$, and in each case parallel rays of light will come to focus $\frac{1}{2}$ meter from the second surface of the lens. By definition, the dioptric power

rays as they leave the lens are convergent to a point one meter away, which is the same as saying that their dioptric value as they leave the lens is $+1D$. At the lens a change in the dioptric value to the extent of $+1D$ has occurred: the incident rays have a value of zero D , the emergent rays have a value of $+1D$. Hence the lens is said to have a dioptric power of $+1D$.

A Simple Means of Calculating the Distance of an Image

A REAL IMAGE.—Knowing the dioptric power of any lens we may easily calculate the distance of an image from the lens if we know the distance of the object. For example,

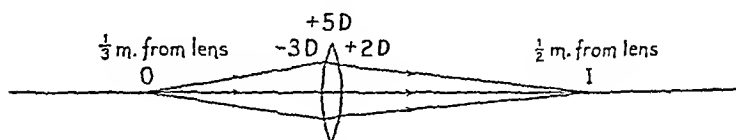


Fig. 198.—Refraction of light by a convergent lens with a real image at I of an object point situated at O . The dioptric value of the emergent light is equal, as in every case, to the sum of the dioptric value of the incident light and the dioptric power of the lens.

suppose an object point is situated at a distance of $\frac{1}{3}$ meter from a lens whose dioptric power is $+5D$ (Fig. 198). All rays divergent from the object point O have a dioptric value of $-3D$ as they strike the lens. Since the dioptric power of

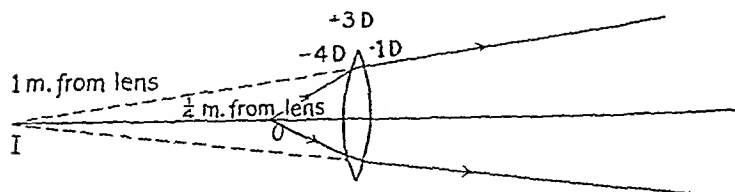


Fig. 199.—Refraction of light by a convergent lens, with a virtual image at I of an object point situated at O

the lens is $+5D$, the emergent rays have a dioptric value of $+2D$ as they leave the lens ($-3D + 5D = +2D$). This means that the rays of light leave the lens converging to a point $\frac{1}{2}$ meter away, and therefore at a distance of $\frac{1}{2}$ meter from

the lens the image will be found. Such an image is *real*, being actually formed by the meeting of convergent rays of light.

A VIRTUAL IMAGE.—But not all images are real. Suppose an object point is situated at a distance of $\frac{1}{2}$ meter from a $\div 3D$ lens (Fig. 199). In this case the dioptric value of the incident rays is $-4D$, since they are diverging from a point $\frac{1}{2}$ meter in front of the lens. The dioptric value of the emergent light is $-1D$ ($-4D \div 3D = -1D$). The emergent rays, being still divergent, will never meet. Their dioptric value being $-1D$, they diverge as if from a point 1 meter in front of the lens, at which point the image is said to be. But in this case the image, being an "as if" affair, is said to be *virtual*. A real image can be formed only by convergent rays of light actually meeting.

The Forms of an Ophthalmic Lens

When we say that a lens has a dioptric power of $\div 1D$, we really mean that the sum of the dioptric power of the indi-

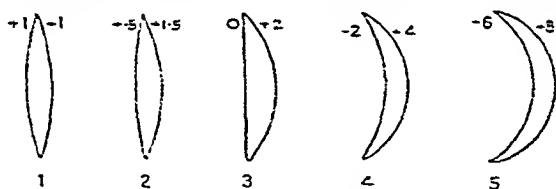


Fig. 200.—The forms of lenses. A $\div 2D$ sphere made up in five different forms.

vidual surfaces equals $\div 1D$. Strictly speaking, the thickness of the lens would also have to be allowed for in determining the dioptric power of the lens as a whole, but for all practical purposes of exposition the thickness of an ophthalmic lens may be considered as having only a negligible effect upon its dioptric power. By distributing the power in various ways over the two surfaces an infinite variety of *forms* for a lens of any given power can be designed. Thus in Fig. 200 the lenses of different forms all have a dioptric power of $\div 2D$. The sum of each pair of surfaces is $\div 2D$, and in each case parallel rays of light will come to focus $\frac{1}{2}$ meter from the second surface of the lens. By definition, the dioptric power

of an ophthalmic lens is the reciprocal of the principal image distance as measured from the rear surface of the lens. By *principal image distance* is meant the distance of the image (real or virtual) formed by incident rays of zero vergence (that is, parallel).

BEST-FORM LENSES.—By thus varying the form of a lens while keeping a given dioptric power it is possible to design a spectacle lens for best optical effect. For example, a deep-curved lens such as the fifth in Fig. 200 would afford a much wider field of clear vision than "flat" lenses like 1, 2 and 3. Deep-curved lenses can be called "clear to the very edge" with greater justice than "flats." Series of spectacle lenses individually calculated for the best possible optical effect in all powers have been designed and are marketed under various names.

Refraction of the Eye

The Three Refracting Surfaces of the Eye.—The eye, like a spectacle lens, has a dioptric power which is equal to the sum of the dioptric power of its individual refracting surfaces (plus a "correction" that must be made for the distances separating the surfaces and for the optical density of the refracting media). The refracting surfaces of the eye are three, namely, the anterior surface of the cornea, the anterior surface of the crystalline lens, and the posterior surface of the crystalline lens. The posterior surface of the cornea is not counted as a refracting surface, since the cornea and the aqueous are of the same optical density and hence no refraction takes place at the boundary surface of these two media.

The Eye Unique Among Optical Systems in Having One Surface of Variable Refractive Power.—But in one very important respect the eye differs from a spectacle lens in having one surface, namely, the anterior surface of the crystalline lens, of variable power. This provision of variability of refractive power exists in order that rays of light entering the eye from objects at different distances may in turn be brought to a focus on the retina. This automatic adjustment of the eye for focusing upon the retina light from objects at different distances is known as *accommodation*.

The Static and Dynamic Refraction of the Eye.—When no accommodation is exerted the refractive power of the eye is at its minimum. This minimum refractive power is conveniently referred to as the *static refraction* of the eye. The increase in refractive power that can be gained by accommodating is known as the *dynamic refraction*.

REFRACTIVE ERRORS AND A SIMPLE SUBJECTIVE METHOD FOR THEIR CORRECTION

Emmetropia, Myopia, Hypermetropia. Spherical Lenses.—An eye is said to be *emmetropic* if, when no accommodation is exerted, incident rays of zero vergence come to a focus on the retina. If an eye has an excess of static refractive power, incident rays of zero vergence come to a focus in front of the retina, and the eye is *myopic*. An eye whose static refraction is insufficient to bring incident rays of zero vergence to a focus on the retina is said to be *hypermetropic*. The excess or insufficiency of refractive power is measurable in diopters. Thus, a hypermetropic eye lacking one diopter of refractive power is said to have one diopter of hypermetropia. This insufficiency of one diopter in the refractive power of the eye may be supplied by a $+1.00D$ spherical lens placed in front of the eye. A *spherical lens* is one whose power is the same in all meridians. Each surface of a spherical lens is generally a portion of the surface of a sphere. Likewise a myopic eye may be corrected by a minus spherical lens of suitable power. Plus lenses are used when the static refractive power of the eye is insufficient; minus lenses are used when the static refractive power of the eye is excessive.

Astigmatism. Cylindrical Lenses.—Sometimes the static refractive power is not the same in all meridians of the eye; in which case the eye has *astigmatism*. An astigmatic eye is always myopic or hypermetropic, or may even be both; for example, it may have an excess of power (myopia) in one meridian, and an insufficiency (hypermetropia) in another. In any eye with regular astigmatism the *principal meridians*, that is, the meridians of greatest and least power, are always at right angles to each other. It should be noted that astigmatism is not a third kind of refractive error on an equal footing with

myopia and hypermetropia but has reference merely to an inequality of refractive power in the various meridians of the eye. Astigmatism may be corrected by a lens having maximum power in one meridian and minimum power in the meridian at right angles. Trial sets are supplied with such lenses in the form of "cylinders" for use in correcting astigmatism. *Cylindrical lenses* have no power along their axis and maximum power at right angles to the axis. The position of a cylindrical lens is indicated with reference to its axis. Thus, a cylinder at axis 90 means that the axis is placed vertically (see Fig. 201).

Objective and Subjective Tests.—The static refractive power of an eye may be measured either objectively or sub-

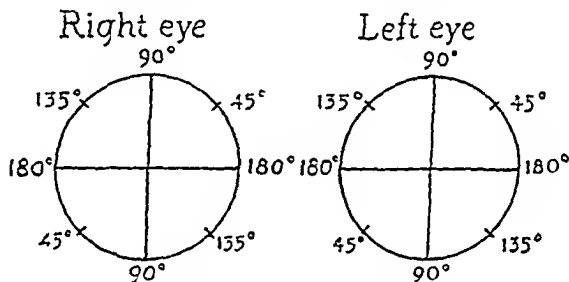


Fig. 201.—Standard notation of cylinders.

jectively. Objective tests, which do not depend upon the patient's interpretation of what he sees, are not within the scope of this paper. They are desirable in most cases and are often necessary. But, on the whole, subjective tests, when properly conducted, are the most dependable. By taking advantage of certain optical phenomena it is easy to determine the refractive error of the great majority of reasonably intelligent persons. The only test charts required for a simple subjective method are a Snellen test chart (such as that pictured in Fig. 202), an astigmatic Fan (such as shown in Fig. 203), and a rotatable Cross (Fig. 204).

The Manifest Refractive Error Measured without the Aid of a Cycloplegic.—A cycloplegic is not required for the measurement of the manifest refractive error. Latent errors of re-

$V = \frac{20}{200}$	E	1
$V = \frac{20}{100}$	F P	2
$V = \frac{20}{70}$	T O Z	3
$V = \frac{20}{50}$	L P E D	4
$V = \frac{20}{40}$	P E C F D	5
$V = \frac{20}{30}$	<u>E D F C Z P</u>	6
$V = \frac{20}{25}$	T E L O P E D	7
$V = \frac{20}{20}$	<u>D E F P O T E C</u>	8
$V = \frac{20}{15}$	L E F O P T C	9
$V = \frac{20}{13}$	10
$V = \frac{20}{10}$	11

Fig. 202.—Snellen Test Chart. At the left of this particular chart is given a scale (in English, not metric, units) of visual acuity. The heavy black horizontal lines would appear on the actual chart as colored, one green and the other red. Their presence is merely for convenience in directing a patient's attention to a particular line of letters ("the line above the red," etc.). (Gifford, "Textbook of Ophthalmology.")

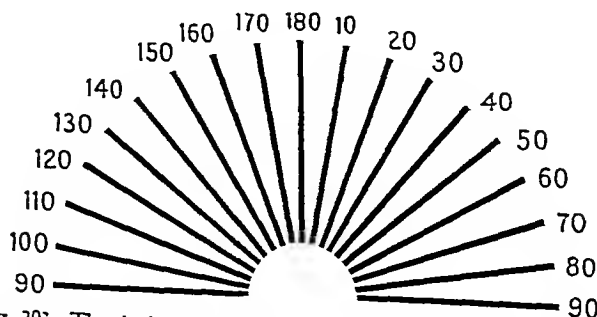


Fig. 203.—The Astigmatic Fan. The notation (in degrees) has reference to the position of the axis of minus cylinders. For example, if an eye which is myopic in all meridians sees the line marked 70 as blackest and most distinct, the measuring or correcting minus cylinder is to be placed with its axis in the 70th meridian. (See Fig. 201.)

myopia and hypermetropia but has reference merely to an inequality of refractive power in the various meridians of the eye. Astigmatism may be corrected by a lens having maximum power in one meridian and minimum power in the meridian at right angles. Trial sets are supplied with such lenses in the form of "cylinders" for use in correcting astigmatism. *Cylindrical lenses* have no power along their axis and maximum power at right angles to the axis. The position of a cylindrical lens is indicated with reference to its axis. Thus, a cylinder at axis 90 means that the axis is placed vertically (see Fig. 201).

Objective and Subjective Tests.—The static refractive power of an eye may be measured either objectively or sub-

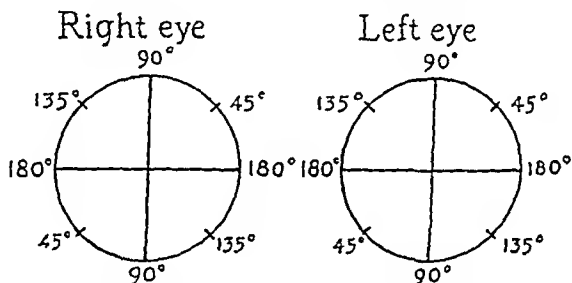


Fig. 201.—Standard notation of cylinders.

jectively. Objective tests, which do not depend upon the patient's interpretation of what he sees, are not within the scope of this paper. They are desirable in most cases and are often necessary. But, on the whole, subjective tests, when properly conducted, are the most dependable. By taking advantage of certain optical phenomena it is easy to determine the refractive error of the great majority of reasonably intelligent persons. The only test charts required for a simple subjective method are a Snellen test chart (such as that pictured in Fig. 202), an astigmatic Fan (such as shown in Fig. 203), and a rotatable Cross (Fig. 204).

The Manifest Refractive Error Measured without the Aid of a Cycloplegic.—A cycloplegic is not required for the measurement of the manifest refractive error. Latent errors of re-

the weakest meridian to make it equal to that of the strongest, or a minus cylinder may be used to decrease the power of the strongest meridian to make it equal to that of the weakest. Astigmatism may be measured and corrected with a plus or a minus cylinder indifferently. Once the power of all meridians has been equalized by correction of the astigmatism, all that is necessary is a spherical lens of the proper power to put the focus upon the retina.

Minus Cylinders Used.—In the subjective method set forth below only minus cylinders are used, regardless of whether the eye is hypermetropic or myopic, or whether it is hypermetropic in one of its principal meridians and myopic in the other. Minus cylinders are used, not because they measure or correct the astigmatism better (they don't!), but because in this particular method they can be used advantageously.

The Determinations Made in the Order of Axis, Cylinder, Sphere.—Any refractive error may be measured if only three determinations are made, namely, sphere, cylinder and axis. In the subjective method now to be explained and outlined these will be determined in the reverse order; that is, the axis of the correcting minus cylinder is first determined with the aid of the Fan, and the power of the cylinder is then determined with the aid of the Cross. If a cylindrical lens does not suffice to bring the light to a focus upon the retina, a spherical lens is also used. In most cases a spherical lens is needed as well as a cylindrical.

The optical phenomena upon which our simple subjective method is based may be understood with the aid of two diagrams (Figs. 205 and 206).

A Cone of Convergent Rays in Eyes without Astigmatism.—Rays of light of zero vergence after passing through the round aperture (the pupil of the eye is usually round, or nearly so) of the optical system of an unaccommodated eye having no astigmatism form a cone of convergent rays. Disregarding for a moment the position of the screen (that is, the retina) which is to receive the rays we may say that these rays will meet at a focal point from which they subsequently diverge. If the retina is anterior to the focal point, the eye is hypermetropic. If it is at the focal point, the eye is

fraction are measurable with a cycloplegic. "Drops" are not usually necessary for the determination of a suitable correction of a patient's refractive error, but in every case the accommodation must be under control at the time of testing. For this reason the eye being tested, if not myopic, is made artificially so by means of a plus spherical lens. In a myopic eye the accommodation is usually well controlled and relaxed

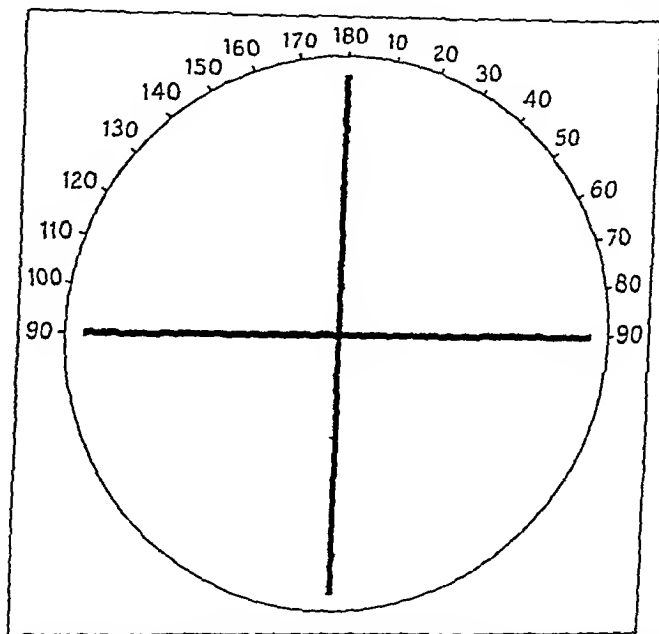


Fig. 204.—The Astigmatic Cross. This rotatable cross is set so that one of its limbs corresponds in direction to the line selected as blackest and most distinct on the astigmatic Fan.

in distant vision, whereas a hypermetropic eye tends to accommodate in the interest of clear vision at distance.

Three, and Three Only, Determinations Necessary.—The refractive error of any eye may be expressed in terms of sphere, cylinder and axis. If regular astigmatism is present a cylinder is required to equalize the power of the various meridians. (Irregular astigmatism is not ordinarily correctible.) A plus cylinder may be used to increase the power of

above about the focus being the point where rays of light meet. In plane 1 (which may be conveniently called a "movable" plane, since it represents any plane anterior to plane 1) the rays in cross section form a horizontal ellipse. In plane 4, which, like planes 2 and 6, is a "fixed" plane, the rays in cross section form a circle. In the movable plane 3, that is, any plane between planes 2 and 4, the rays in cross section form a horizontal ellipse. Likewise in movable planes 5 and 7 the rays in cross section form a vertical ellipse. The position

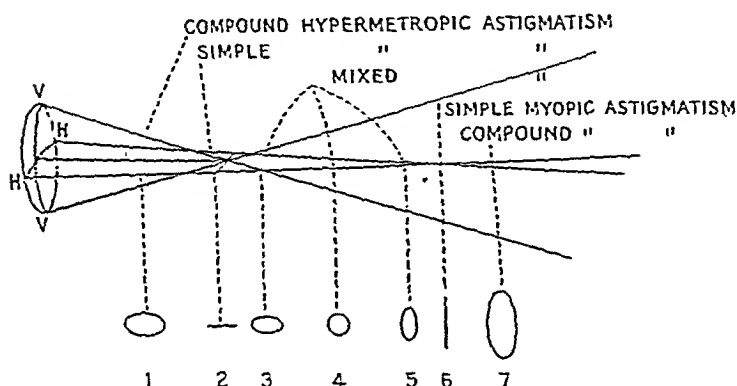


Fig. 206.—Refraction by an astigmatic optical system. The seven possible positions of the retina with respect to the focal lines in an eye with astigmatism. The vertical meridian, VV , of the system is more curved than the horizontal, HH . At 2 the rays passing through the most curved vertical meridian are brought to a focus (horizontal line); at 6 in the rays passing through the least curved horizontal meridian are brought to a focus (vertical line). The numbers 1, 2, 3, 4, 5, 6 and 7 show the seven characteristic cross sections of the conoid of Sturm.

of the vertical and horizontal lines and ellipses is reversed if the greatest power is in the horizontal meridian instead of in the vertical.

Astigmatism with and against the Rule. Oblique Astigmatism.—When the power is greatest in the vertical meridian or approximately vertical meridian, the astigmatism is said to be *with the rule*; when the power is greatest in the horizontal or approximately horizontal meridian, the astigmatism is said to be *against the rule*. But the principal meridians, that is, the

emmetropic. If it is behind the focal point, the eye is myopic (Fig. 205).

The One Condition Necessary for a Sharp Retinal Image.—A perpendicular cross section of the cone of convergent light or of the cone of divergent light has the form of a circle. A cross section has the form of a point only at the common apex of the cones. Any point of an object cannot be imaged upon the retina as a point unless the retina is at the apex of the cone of convergent light. If the retina is elsewhere each point of the object will have corresponding to it upon the retina a circle, and the retinal image will therefore be blurred.

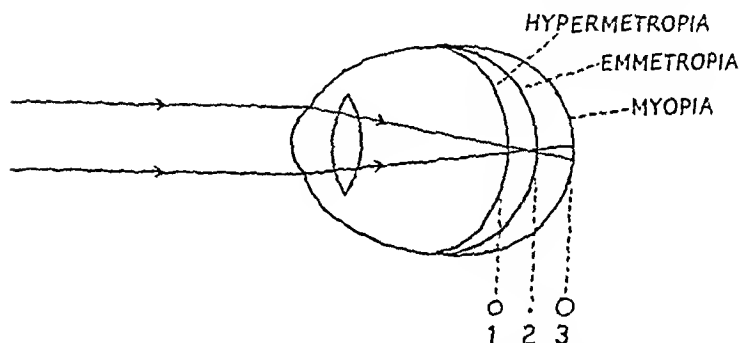


Fig. 205.—The three possible positions of the retina with respect to the focal point in an eye without astigmatism. The numbers 1, 2 and 3 show different sections of the beam after refraction.

A Conoid of Sturm in Astigmatic Eyes. A Sharp Retinal Image Not Possible in Astigmatism.—Rays of light of zero vergence after passing through the round aperture of the optical system of an astigmatic eye form a *conoid of Sturm*. Since the power of the optical system is not the same in all meridians, the rays will never all meet at a point as in the case of an eye without astigmatism. If an eye has its greatest power in the vertical meridian (and consequently its least power in the horizontal meridian), the conoid as seen in successive cross sections has the form shown in Fig. 206. In plane 2 the rays meet to form a horizontal line, and in plane 6 they meet to form a vertical line. These lines are called *foci*, or *focal lines*, and constitute the one exception to what was said

even in an emmetropic eye or by a lens designer who would design a perfect optical system. Not all the rays from a point meet at a corresponding point after refraction. Some of the rays are always aberrant. The existence of aberrations in any optical system must be admitted, but for practical purposes and without serious vitiation of the fundamental principles of refraction herein outlined their existence may be disregarded.

The Nature of the Images in Anisotropia.—In simple hypermetropia and myopia each point of the object has a circle corresponding to it upon the retina. In astigmatism each point

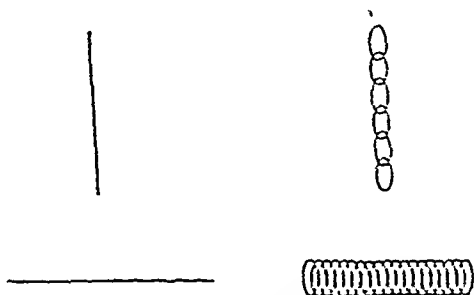


Fig. 207.—Vision in astigmatism. At the left, two lines as seen by an emmetropic eye. At the right, the same two lines as they would appear (upon analysis) to an eye having compound myopic astigmatism with the rule. Both lines appear to the eye as blurred, the horizontal more than the vertical. The retinal image of each line is analyzable into an infinite number of overlapping vertical ellipses all identical in shape and size.

of the object has corresponding to it upon the retina a line, an ellipse, or a circle, but never a point.

The Appearance of Horizontal and Vertical Lines in Astigmatism.—To an eye having compound myopic astigmatism with the rule a vertical line looks clearer than a similar horizontal line, because, according to the conoid of Sturm, each point of the object has corresponding to it on the screen a vertical ellipse. Hence a horizontal line can be analyzed into an infinite number of overlapping vertical ellipses, and therefore will appear broader than a vertical line which is likewise analyzable into an infinite number of overlapping vertical ellipses (Fig. 207).

meridians of greatest and least power, may be anywhere, and sometimes therefore the astigmatism is *oblique*. The direction of the lines and ellipses in the conoid of Sturm always correspond to the direction of the principal meridians of the eye.

It should be noted that this threefold classification is not one of different kinds of astigmatism. There is no difference in *kind*. The classification is merely a convenient way of indicating the direction of the principal meridians of the eye, or, what amounts to the same thing, the direction taken by the two focal lines.

Another Classification of Astigmatism.—The retina may occupy any one of the seven planes of the conoid of Sturm. If the retina is in plane 1 the eye is said to have *compound hypermetropic astigmatism*, that is, the eye is hypermetropic in all meridians. If the retina is in plane 2 the eye has *simple hypermetropic astigmatism*; this is equivalent to saying that one of the principal meridians of the eye is emmetropic and the other is hypermetropic. If the retina is in plane 3, 4 or 5, a condition of *mixed astigmatism* results; one of the principal meridians is hypermetropic and the other is myopic. Similarly, a condition of *simple myopic astigmatism* is present when the retina is in plane 6, and the refractive condition is *compound myopic astigmatism* when the retina is in plane 7.

It should be noted likewise that in this fivefold classification there is no difference in the kind of astigmatism. The classification serves merely to indicate the position of the retina with respect to the conoid of Sturm. The conoid itself, which is the optical manifestation of the astigmatism, may be identical in the case of all possible positions of the retina.

A Point-for-point Image Possible only in Emmetropia.—For an object to be seen clearly a point-for-point image of it must be formed upon the retina. An image is said to be *point-for-point* when each point of the object has corresponding to it upon the screen (that is, the retina in the case of the eye) a point. Such a correspondence is possible only when the eye is emmetropic.

A Point-for-point Image Really Impossible Anyhow. Aberrations Admitted and Dismissed.—Unfortunately, an unfailing point-for-point correspondence is an ideal never achieved

with its axis in the proper meridian. One line of the Cross is first placed so as to correspond in direction with the most distinctly seen line of the Fan. The minus cylinder that equalizes the two lines of the Cross is the correcting cylinder.

The Determination of the Sphere.—If the astigmatism has been properly corrected by this method, a condition of simple myopia then results. Minus lenses of gradually increasing power are placed in front of the eye until the sharpest possible vision is obtained on the Snellen chart. The correcting spherical lens is determined by adding the power of the final minus spherical lens to that of the lens (if any) used at the outset to make the eye sufficiently myopic in all meridians.

Insufficient Dynamic Refraction a Cause of Difficulty in Near Vision.—An emmetropic eye, or an eye whose static refraction has been carefully corrected, may see clearly and comfortably at distance, yet may have poor vision and accommodative strain at near. Clear comfortable vision at near cannot be expected unless the amplitude of accommodation is sufficient. Tables or graphs of the amplitude of refraction are given in treatises on refraction. Since the amplitude of accommodation decreases with age, the dynamic refractive power of our eyes tends to become insufficient as we get older. When the dynamic refractive power is insufficient, plus lenses are used to supply the insufficiency. An insufficiency of refractive power, whether of the static or of the dynamic refractive power, is always corrected with plus lenses. Insufficiency of accommodation is similar to hypermetropia in that the same optical treatment is accorded to both.

Three Diopters of Plus Power Needed by an Emmetropic Eye for Clear Vision at $\frac{1}{3}$ Meter.—Close work, such as reading or sewing, is commonly done at a distance of $\frac{1}{3}$ meter. Near-point tests are often made on the assumption that work is done at this distance, since rays of light diverging from a distance of $\frac{1}{3}$ meter have a vergence of $-3D$ when they reach the eye. Three, being a whole number, is easily dealt with in making calculations. If the vergence of the incident rays is $-3D$, then in the case of an emmetropic eye three diopters of plus power are needed to bring the light to a focus on the retina; that is, the divergence of $-3D$ must be over-

This Appearance the Basis of a Subjective Method for Correcting Astigmatism. Myopia, Real or Artificial, the Necessary Starting Point.—Advantage is taken of the appearance of one line running in one direction as compared with that of other lines running in other directions in determining the presence of astigmatism and the position of the axis of the correcting minus cylinder. But in order to take full advantage of this optical phenomenon it is necessary for the eye that is being tested to be myopic in all meridians. Hence the first step in measuring a refractive error is to make the eye sufficiently myopic (if it is not already so) in all meridians. The hypermetropic eye may misbehave under test, because exertion of accommodation may move the conoid of Sturm so that any one of the seven planes may fall upon the retina, whereas in an eye with compound myopic astigmatism the retina is necessarily in plane 7 whether accommodation is exerted or not. For the purpose of determining the presence of astigmatism and the position of the axis of the correcting minus cylinder, an eye may be said to be sufficiently myopic in all meridians if all the lines of the Fan are blurred, but one of these is blurred only slightly. An eye may be put in this state by placing in front of it a strong plus lens and then gradually reducing the plus power until one of the lines stands out fairly well. If, as the plus power is reduced, all the lines look alike, the absence of astigmatism is inferred, and the lens correcting the refractive error is the highest plus or lowest minus spherical lens that gives clearest vision on the Snellen chart.

The Determination of the Axis.—But if, as the plus power is gradually reduced, one of the lines of the Fan comes out clearer than the others, the presence of astigmatism is established. The axis of the correcting minus cylinder is determined by the line of the Fan which stands out clearest, and may be read directly from the Fan if the lines are numbered as shown in Fig. 203.

The Determination of the Cylinder.—When the position of the axis of the correcting minus cylinder has been determined, the amount of the astigmatism may be measured by equalizing the lines of the Cross with a minus cylinder placed

with its axis in the proper meridian. One line of the Cross is first placed so as to correspond in direction with the most distinctly seen line of the Fan. The minus cylinder that equalizes the two lines of the Cross is the correcting cylinder.

The Determination of the Sphere.—If the astigmatism has been properly corrected by this method, a condition of simple myopia then results. Minus lenses of gradually increasing power are placed in front of the eye until the sharpest possible vision is obtained on the Snellen chart. The correcting spherical lens is determined by adding the power of the final minus spherical lens to that of the lens (if any) used at the outset to make the eye sufficiently myopic in all meridians.

Insufficient Dynamic Refraction a Cause of Difficulty in Near Vision.—An emmetropic eye, or an eye whose static refraction has been carefully corrected, may see clearly and comfortably at distance, yet may have poor vision and accommodative strain at near. Clear comfortable vision at near cannot be expected unless the amplitude of accommodation is sufficient. Tables or graphs of the amplitude of refraction are given in treatises on refraction. Since the amplitude of accommodation decreases with age, the dynamic refractive power of our eyes tends to become insufficient as we get older. When the dynamic refractive power is insufficient, plus lenses are used to supply the insufficiency. An insufficiency of refractive power, whether of the static or of the dynamic refractive power, is always corrected with plus lenses. Insufficiency of accommodation is similar to hypermetropia in that the same optical treatment is accorded to both.

Three Diopters of Plus Power Needed by an Emmetropic Eye for Clear Vision at $\frac{1}{3}$ Meter.—Close work, such as reading or sewing, is commonly done at a distance of $\frac{1}{3}$ meter. Near-point tests are often made on the assumption that work is done at this distance, since rays of light diverging from a distance of $\frac{1}{3}$ meter have a vergence of $-3D$ when they reach the eye. Three, being a whole number, is easily dealt with in making calculations. If the vergence of the incident rays is $-3D$, then in the case of an emmetropic eye three diopters of plus power are needed to bring the light to a focus on the retina; that is, the divergence of $-3D$ must be over-

come by a like amount of plus power. This plus power may be supplied either by the dynamic refraction of the eye or by a plus lens or by a combination of the two.

The "Reserve" Portion of Accommodation.—Generally one-half to two-thirds of the total amplitude of accommodation is available for continued use. If a greater part of the accommodation is made to work continuously for any length of time, the eye fatigues unduly. We say accordingly that from one-third to one-half of the accommodation must be kept in reserve. For example, if we are emmetropic either naturally or with the aid of glasses, and our amplitude of accommodation is 7D, as at the age of thirty, we may expect to read comfortably at a distance of $\frac{1}{2}$ meter, since the demand upon accommodation will be less than one-half the amplitude.

An Emmetrope's Difficulty in the Forties, and How It Is Met.—But an emmetrope as he gets on in the forties generally begins to have trouble with near vision. At forty-five the amplitude of accommodation is about 3.50D. Although this amplitude is sufficient for overcoming a vergence of -3 D, yet too great a part of the accommodation must be used for reading comfortably at $\frac{1}{2}$ meter. If from one-third to one-half of the accommodation is to be kept in reserve only about 1.50D is available for use. Hence the remaining $+1.50$ D must be supplied with a plus lens. The correction for near vision is determined by adding the $+1.50$ D to the correction for the static error in the case of myopia or hypermetropia. Thus the distant correction of a 1D myope is -1 D, and the near correction, as calculated for a man whose amplitude is 3.50D, would be -1 D $+ 1.50$ D or $+.50$ D.

A Final Word of Caution.—Limitation of space has prevented this from being more than a very sketchy outline of a few simple principles. In charity, it should be remembered that the suppression of many important facts of optics and refraction has been due to the requirement of brevity. Unfortunately, a suppression of truth sometimes results in a real or apparent perversion of truth. A much larger treatise would be required for adequate presentation of the art and science of refraction. But it is hoped that the optical principles herein outlined will serve as basis upon which the student may build a sound knowledge of refractive technic.

TROPICAL MEDICINE IN THE UNITED STATES TODAY

GEORGE CHEEVER SHATTUCK, M.D.*

What Is Tropical Medicine?

In the broadest sense, tropical medicine comprises all that is known of the etiology, prevention, diagnosis and treatment of all of the diseases which may originate in the tropics.

The physician practicing in the tropics is concerned with diseases of several categories. *Firstly*, there is a small group of diseases which can originate only in the tropics. *Secondly*, there are many diseases of more or less cosmopolitan distribution which are classed as tropical because they are more prevalent in the tropics than in the temperate zones. *Thirdly*, there is a large number of diseases of nearly world-wide distribution which are common in temperate climates and which may be encountered in the tropics as well.

Textbooks of general medicine deal primarily with the diseases of the third category, briefly with those of the second category, and may not even mention those of the first category. On the other hand, textbooks of tropical medicine deal at length with the diseases of the first and second categories but not with those of the third.

In the United States it is expedient to assign to the specially trained health officer, who is assisted by the sanitary engineer, the task of protecting the health of the public, and to divide responsibility for the care of the sick among medical and surgical practitioners, hospital administrators and other medical specialists.

In tropical countries, where physicians are comparatively scarce, there are few medical specialists except in some of the larger cities. Therefore every physician is expected to be competent in nearly all branches of curative medicine and in

* Clinical Professor of Tropical Medicine, Harvard Medical School and Harvard School of Public Health; Consultant in Tropical Diseases, Boston City and Massachusetts General Hospitals.

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Where Does Tropical Medicine Stand Now?

The comprehensive courses in the laboratory diagnosis of tropical diseases, which used to be given for graduate students under the direction of Dr. Richard P. Strong, at the Harvard Medical School, have been drastically curtailed in recent years. Furthermore, attempts to develop the teaching of tropical medicine in San Francisco have been relatively unsuccessful and little was accomplished along these lines at Tulane University in New Orleans until 1941 when additional funds for the purpose became available. Very recently, the University of Puerto Rico has improved its facilities for teaching and research in tropical medicine. Most of the American physicians who have wanted special instruction in tropical medicine in recent years have taken the course at the School of Tropical Medicine in London. The number so trained, of course, is small.

Since the United States entered the present World War, brief courses in tropical medicine and in tropical hygiene and sanitation have been provided for newly inducted medical officers. Because of the urgent demand for more medical officers in the field, this instruction has necessarily been inadequate. Our soldiers are being sent to widely scattered stations in the tropics. But the medical personnel of our fighting forces is being recruited from practitioners who know little or nothing about tropical medicine. A striking illustration of ignorance was afforded recently by the intelligent ranking officer of a medical unit who, on the eve of departure for military service, asked to be told in a few words what he should know about sanitation for the tropics.

I understand that medical schools have very recently been officially requested to teach more about tropical medicine not only to their undergraduate students but also to offer additional short courses in the subject to prospective medical officers.

What Should Be the Scope of Instruction in Tropical Medicine?

Just at this time, when the courses for medical students are being telescoped in order to graduate more physicians as soon as possible, nothing can be added to the curriculum

preventive medicine as well. Consequently, the physician in the tropics needs as broad and as thorough a training as it is possible for him to obtain.

The usual British or American textbook of general medicine does not deal in detail with the prophylaxis of infectious diseases. The standard textbooks of tropical medicine, on the other hand, give considerable space both to public health measures for controlling the important infectious diseases of the tropics and to personal prophylaxis. Thus, it is evident that the average practitioner must look beyond the textbook of general medicine for information about the commoner of the tropical diseases in the United States. It is equally clear that if he is to recognize and to treat the tropical diseases of less common occurrence in the United States, he should have studied tropical medicine.

Why Has Instruction in Tropical Medicine Been Neglected in the United States?

The reasons for the neglect of instruction in tropical medicine fall naturally into several categories.

1. In medicine, as in many other fields, Americans have been focusing their attention on the home front and few of our physicians have become interested in the disease problems of other countries. In consequence, aside from the needs of the Army and the Navy, which for a number of years have been providing special instruction in tropical medicine for their own personnel, there has been little recognition of the value of instruction in tropical medicine.

2. Some of the important tropical diseases, for example *malaria*, *hookworm*, and *amebic dysentery*, are so common in our southern states that they are dealt with in the undergraduate medical courses of the southern medical schools. With few exceptions, these schools have not undertaken to offer advanced instruction in tropical medicine.

3. There has been little opportunity in recent years for physicians from the United States either to make a living in a tropical country or to obtain an academic position with adequate salary as a teacher of tropical medicine in the United States.

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without subtracting from it something else which is valuable. Consequently, the new instruction in tropical medicine which is to be injected into the curricula must be confined to the barest essentials. This means, in my opinion, that most of the time assigned to tropical medicine should be devoted to instruction in the *laboratory diagnosis of the tropical diseases of major importance*. The student should learn the laboratory technics which are needed to confirm or to exclude a diagnosis of *malaria, dysentery, yellow fever, plague or cholera*. When it is not possible to provide for him this laboratory training, prepared specimens should be demonstrated and studied. Lectures are useful for the purpose of presenting important facts in perspective as well as calling attention to recently acquired knowledge. The lecturer should not attempt, however, to present material which can easily be acquired from a textbook. Required reading should supplement the lectures and demonstrations.

An editorial in the *American Journal of Public Health* (June, 1942, page 645) has stressed the overwhelming importance in most of the tropical countries of malaria and dysentery. I am heartily in accord with this view. Therefore, I believe that, whatever else may have to be passed over, the *diagnosis, treatment and means of prevention of the malarias and of the dysenteries* should be taught.

Physicians who have not been especially concerned with tropical diseases may fail to realize the difficulty of passing judgment on an obscure case of possible malaria or of amebiasis, and they rarely appreciate the fact that, in such cases, they should seek the help of a well-trained and experienced protozoologist.

Doubtless more specialists trained in the laboratory diagnosis of tropical diseases are needed now for military service; certainly more of them are needed at our civil medical centers; and, after the war is over, when soldiers and civilians are returning in great numbers from the tropics, facilities for the prompt recognition of tropical diseases will be in even greater demand.

WHAT CAN PSYCHIATRY DO TO PREVENT NEUROSIS?

MERRILL MOORE, M.D.*

THE problems of mental hygiene are essentially the same everywhere for everyone has the same need to be happy, useful and secure. The human spirit is truly universal and the drives, motives and wishes everywhere are basically identical. Poets, philosophers and theologians have known this for a long time, but it has been taken into account officially by physicians only since the rise of psychiatry.

Even normal people need to be taught, however, and can learn much from those whose personal limitations cause them to fail to live effectively.

There was a time when the distinction between normal and abnormal was believed to be as clear as the difference between black and white. Those days are gone forever. A hundred years ago it was generally believed that people were either sane or insane. Now people realize that there are fragments of sanity in the most insane and, conversely, fragments of insanity in the most sane. Today an effort is made to use the good qualities of both types in ways that are satisfactory to the individual and useful to others.

But one distressing question always occurs to thoughtful people whenever they see a mentally ill person, namely: What might have been done to prevent this? How could this suffering have been avoided? No one knows the answer exactly. This is the question every psychiatrist asks himself sooner or later as he works with adult patients. It is obvious that the insane person is in the end-stage of a condition which may result from previous difficulties or their mismanagement,

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things that have never happened or that could not happen. The origins of anxiety may be many, but their roots usually go back to childhood and sometimes can be brought by psychiatric treatment to the level of conscious understanding. Even if the patient is unable to recognize the original fears and their causes, the doctor is often able to spot them and may sometimes be able to help the patient's symptoms without furthering his basic understanding.

Hysteria

Hysterical people do not always simply cry, or lose control of their emotions, or shriek at the sight of a mouse, as common usage of the word might lead one to suppose. The hysterical person, in certain situations, may lose one or more of his faculties without apparent physical reason, or he may develop symptoms by the mechanism of conversion of his nervous energy. Some of the miraculous cures may have been such cases. A person with an hysterical paralysis, for example, may throw away his crutches and walk without them once he is thoroughly convinced by suggestion that he can walk. Persuasion or emotional reeducation may enable him to walk again when physical methods of treatment have failed. Many cases of industrial injury in patients believed to be malingerers may actually be cases of hysteria. Hysteria can also be described as a temporary splitting or dissociation of the personality under tension or conflict. It has also been described as the disease that takes the form the patient thinks it should, or emotion gone off the track, or childish behavior in an adult. Apart from the nervous instability it seems to indicate, or the immaturity of character it sometimes betrays, neurotic symptoms or behavior also seem to have a personal significance or a symbolic meaning. Then, too, usually a neurosis confers a secondary gain. Furthermore, some people maintain by habit a neurosis which was originally profitable to them even long after the advantages have disappeared.

Hypochondriasis

Everyone has acquaintances or relatives who are continuously complaining of one ailment or another for which a

and which could have happened a long time ago. Many psychiatrists think, in their daily work, as they struggle with the problems of an adult neurotic: "How did it happen that this person was ever allowed to develop such an extreme degree of neurosis? Why wasn't something done about it sooner? Certainly when this man was in college, or when this woman was in high school, or in his home or school before that, someone might have done something to prevent some of this unnecessary suffering."

NEUROSES

A neurosis or psychoneurosis, so-called, is a condition that might be classed somewhere between normality and a psychosis, or insanity; though no one knows precisely whether there is a real or only an apparent similarity between a neurosis and a psychoneurosis. For much remains to be learned about neuroses; a great deal can be said about the relation between organic and functional factors in an individual case of neurosis, but so far, general conclusions in regard to these matters are not clear. There is a great need to learn more about the physical basis of neuroses. Observers can describe how neuroses appear, and it is possible to observe in individual patients the situations and events which seem to contribute to the development of a neurosis. There seem to be enough similarities in the histories of psychoneurotic patients to justify the assumption that the background helped to produce or precipitate certain symptoms, but the type of difficulties that so-called neurotic individuals encounter fall into several quite distinct groups. It appears that different kinds of neurotic reaction can occur in one individual, and people may suffer varying degrees of neurosis just as one person may have a mild head cold while another may have pneumonia when infected by the same germ.

Anxiety Neurosis

"Anxiety neurosis" is the name given the most obvious type of neurosis on account of its most obvious symptom. In this state an individual worries unduly about simple affairs to an extent that affects all his behavior. He may worry about

of mentally ill persons. One may learn from these histories what not to do and possibly what should be done in caring for the growing child in his home and early school days to prevent the formation of neurotic patterns of behavior and emotional expression. Everything we learn from the observation of the mentally ill in hospitals and from the treatment of neuroses in private practice indicates that more attention should be given to the growing mind of the child by parents and teachers early, rather than later care *after* obvious mental disorders have developed. Principles that are well known in horticulture might well be applied to the rearing of children. Good mental hygiene in its application is much like good gardening. "As the twig is bent, so is the tree inclined." Some persons who deal with children seem to have the same kind of "green thumb" a good gardener has.

If this view is taken, one can look back and see many points along the line where much might have been done to prevent the development of neurotic personalities with their extreme and unnecessary psychic suffering. It is this suffering and the attendant frustration that lead to fatigue and breakdowns, to physical and mental illness. One can often see at the time it happens the precise point at which an individual goes "off the track" or fails to develop satisfactorily, or develops in a peculiar way; just as one can sometimes see in retrospect the situation or the occasion when this occurred as well as some of the factors or conditions that may have deranged or may have retarded normal development, or may have otherwise impeded or upset the growth of a child into a happy and useful man or woman. It is quite possible that much more could be done to prevent or correct these obstructions and derangements. I refer especially to giving the child more assistance in his emotional development; and not attending only to his intellectual development, which is so easy to measure and observe and to which in the past so much attention has been given by schools and colleges. At the same time, more attention might be given to the inner world of the child; to his fears and to the development of his courage, independence and self-control.

physician can find no physical cause. Hypochondriacs are often the object of ridicule and are sometimes not taken seriously even by their family doctors. Their symptoms may be regarded as amusing or irritating by their family, or eccentric by their friends. However, they do suffer. First, they suffer from their fancied illness, and secondly, from their partial realization that the condition of which they complain is not the actual ailment, or their entire difficulty.

A somewhat similar form of neurosis is called *neurasthenia*. This differs from hypochondriasis in that the patient suffers from weakness to such a marked degree that he cannot carry out any activity. He may even be too weak to think.

Compulsion Neurosis

Another type of neurosis is the *compulsive tension* state. Shakespeare has given a good picture of some features of a compulsion neurosis in the character of Lady Macbeth as demonstrated when she continuously washed her hands in the hope of thus erasing her shame. Frequent hand-washing or general overfastidiousness is often a symptom of subconscious feelings of guilt. One patient I recall, for example, always held a piece of paper over a doorknob when opening a door so as not to be contaminated by germs that might be on it.

There are other types of compulsion that have nothing to do with cleanliness. Certain people sometimes go back and test a door three or four times after locking it, "just to be sure" even though they discovered the first time that it had actually been locked. Children are apt to go through a compulsive stage which they show by touching every railing or fence post they pass, or by trying not to step on the cracks in the sidewalk as they walk along. This is not abnormal in children, but when adults carry such patterns of ritualistic behavior to extremes, they can interfere seriously with more important affairs.

PREVENTIVE PSYCHIATRY

If mental hygiene develops and if it is successful in preventing mental illness, this will probably come about by using the information gained from the study and treatment

of mentally ill persons. One may learn from these histories what not to do and possibly what should be done in caring for the growing child in his home and early school days to prevent the formation of neurotic patterns of behavior and emotional expression. Everything we learn from the observation of the mentally ill in hospitals and from the treatment of neuroses in private practice indicates that more attention should be given to the growing mind of the child by parents and teachers early, rather than later care *after* obvious mental disorders have developed. Principles that are well known in horticulture might well be applied to the rearing of children. Good mental hygiene in its application is much like good gardening. "As the twig is bent, so is the tree inclined." Some persons who deal with children seem to have the same kind of "green thumb" a good gardener has.

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A CONCRETE PROGRAM OF MENTAL HYGIENE

Here are a few specific matters that need more attention in a concrete program of mental hygiene. First of all, however, mental hygiene needs to be outlined in forms which its exponents can use more practically. Thus I would begin by mentioning these points, each of which can be emphasized and can be applied in daily life.

What the Obstetrician Can Do

The personality in pliable form begins at birth. Many people have wondered how much the so-called "birth trauma" or the unpleasant physical sensations of being born affect the child's future outlook on life. This is a point about which we can obviously never have much first-hand information. For this reason some physicians choose to discount it, since everyone was once born and by approximately the same process. Nevertheless, the obstetrician is very important to both the mother and the infant. A baby is completely at the mercy of the neuroses of his parents and the neurosis of anyone else who may be in contact with him. Therefore, it is particularly important that both his parents be as placid and as constructive as possible during the early days of his infancy. The obstetrician can contribute significantly to this by reassurance and encouragement, even by suggestion, though it may also be said that the obstetrician probably has his hands full taking care of the mother physically, and that he cannot be expected to concern himself too much with her mental ups and downs. He is, however, in a better position than anyone else to recognize whatever emotional problems the mother may have, and he can consider referring her to a psychiatrist if he feels the problem is more than he wishes to handle.

Every psychiatrist has listened for hours to the complaints of neurotic women about their reproductive functions. From this some are led to believe that physicians should give more reassuring psychotherapy to pregnant women as an essential part of prenatal care because of their fears and the extreme susceptibility to suggestion that is often seen during pregnancy. This psychotherapy should be done intelligently and

it will naturally differ in individual cases. The mental state of the mother during pregnancy affects the child's attitude indirectly even though not genetically. The old wives' tales, quaint though they are, meant something. A neurotic girl may tell you that she has always been afraid of snakes because her mother was frightened by a snake while walking in the garden when she was carrying her daughter. This girl has been conditioned to believe that she is inevitably marked. What actually happened was that a choice story in the family repertoire was the one about the snake that scared Mother. And Mother told the story so often that the daughter grew up to believe it as a fact. Even more important is the experience that from earliest childhood this patient saw her mother react with fear at the idea of a snake, and she therefore assumed that this was a suitable female reaction. Analogous stories and beliefs, and episodes in the family saga, are often even more far-reaching in their effect on a child's personality and attitudes. These things can build up pictures or images in the child's mind to which later on he tends to react with fear. It is a kind of unhealthy reflex conditioning that occurs in the nursery. We often encounter it in treating adult hysterical patients. We need to know more about the fears of children and to pay more attention to them. They are the eggs from which the later neuroses hatch.

Of course there are many people who take to parenthood naturally, and fortunately there are many strong, maternally-minded women who have no more need of reassurance than a mother cat about to have kittens. (But even a mother cat, to be sure, does need some reassurance.) These strong womanly, maternal and stable women are not the ones that usually breed neurotics.

What the Pediatrician Can Do

The next important step in taking care of a child is to provide him with a good pediatrician. The pediatrician's primary importance in the child's life is to assure for him as good physical health as possible. It is not yet known what, if any, are the physical factors in neuroses; but it is a fact that physical illness is a drain on the resources of the whole personality.

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prefer fact, but every child should be offered some of each. A child needs every possible chance to learn to distinguish between fact and fantasy. Reading can afford him valuable opportunities along this line.

In Regard to Sex Education.—In regard to the sex education of children (another topic that deserves a monograph), there is no magic formula. Solomon realized that when he said: "There is no earthly way by sage advice to save the fool from his folly." But one important point may be kept in mind: parents should not overstimulate the child's sexual interest by giving more information than the child wants. And when children do ask for information directly or indirectly, they should be told the truth, or as much as they can understand, in words they can grasp. Many parents fail to recognize or take seriously requests for sex information made by their preschool children. If the subject is dealt with simply and impersonally at the time that questions are first asked, many adolescent problems might be avoided. For example, it is an unnecessary and severe shock for a girl to begin to menstruate without ever having heard of the function, yet this happens all too frequently. There is no need for such a condition to continue to exist.

How the School and Teacher Can Help

An important event in the child's life is the beginning of school. Unfortunately, the ideal school does not exist any more than the ideal world exists, although many excellent educational programs have been developed which give due consideration to mental hygiene needs. Generally speaking, it may be said that one of the school's greatest potential defects is the teacher who is teaching because she must and not because it is the career she chose. Such a teacher usually manages to convey some of her general dissatisfaction or her resentment to her pupils with resultant and varying degrees of derangement in the development of their personalities. But a teacher who really has a child's interest at heart can accomplish a great deal quite unaided. Alfred Adler's writings have helped many parents and teachers in their efforts to understand the problems with which they have to deal.

Illness leaves the individual handicapped to cope with whatever emotional problems may arise. Here again, the pediatrician, like all other physicians, may find it necessary to use psychotherapy in his treatment of the child and the parent. Many parents need to be reassured about their children because the parents themselves are already suffering from an anxiety neurosis. If the parents have good outside help, they are better equipped to avoid damaging the child by their own neurotic behavior. Most parents have not the faintest idea of any such possibility, but it is an important fact that should not be forgotten or ignored.

Children seem to get their neuroses from their parents. A neurosis is obviously not an infectious disease, but it is certainly communicable from adults to a child. In connection with this point every parent and teacher and every physician in America should read one book which has superbly emphasized this basic idea of mental hygiene. It is "The Inner World of Childhood" by Frances G. Wickes, whose essential thesis is that children understand how parents feel without being told. The reading of this book and the proper assimilation of its contents have proved to be the turning point toward better relations in many families I have known. In a few words it shows how children feel and how children sense and react to the feelings of older people around them, even at a very early age. The truly effective parent is the one who is able to take a long-range view of his child's development as an individual.

What Children Should Read.—Parents often ask what they should read to their children or give the children to read. In general, it is a bad idea to volunteer to tell children horror stories, not because of the manifest content of the story itself but on account of the latent aggression or anxiety which the child may sense in the parent or in the home situation. A peaceful and fundamentally friendly parent can usually read the goriest classics of children's literature to a child without any disturbance; but latent fears are sometimes stirred up by these stories. In reading to children or giving them books to read to themselves, it is important to offer them a balanced diet. Some children prefer fantasy and fiction while others

prefer fact, but every child should be offered some of each. A child needs every possible chance to learn to distinguish between fact and fantasy. Reading can afford him valuable opportunities along this line.

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The ideas of individual psychology can easily and often profitably be adapted to the needs of teachers and parents.

But there are many children whose problems are so severe that it is impossible for any school to cope with them without direct psychiatric help. For these children the habit clinic is of great value. In a community where there are *habit clinics* or *child guidance centers* the school can serve as a connecting link between the child's home and the guidance center. If the teacher is sufficiently aware of the child's problems, the neurosis may be correctible and a solution may be reached with outside aid. Parents who are accustomed to the neurosis of their own child often fail to realize that their child has any unusual problem or may need any assistance. This is especially true when there are no other children in the family. Sometimes, in a one-child family, if the child fails to make progress or progresses in the wrong direction, the symptom is not recognized. Sometimes normal progress is greeted with amazement as a rare phenomenon. In either case, the child's life outside of the home is apt to be extremely difficult since his position there is so different from what it was in a one-child home where there were no comparisons or standards. A succession of children provides the parent with approximate standards for comparison; but any parent is likely to forget what one child did when he was seven; and two or three, or even four children are not really a big enough group to serve as examples. The experienced teacher who is familiar with many children of about the same age level knows what can reasonably be expected of a child at a given age and what are the normal variations within these limits.

The Value of Parent-Teacher Organizations.—In the absence of child guidance centers, groups of parents or parent-teacher associations can often serve in part the same function, although these agencies can never be particularly helpful to the child who actually needs a doctor—the child whose behavior difficulties are traceable to chorea, for example. Such a child, of course, needs medical treatment or supervision. But slight deviations from standard behavior can often be corrected if steps are taken promptly and early. Parent-

teacher organizations help to make parents and teachers aware of problems and stimulate interest in their solution.

A Balanced Plan.—Even the parent of the normal child should take a hand in planning the child's daily life. If the parent has matured satisfactorily, he should be able to judge whether there is a reasonable balance of work, play and rest. This balance is rarely the same for any two children, although children tend to fall into approximate groups. These categories do not always follow family patterns. There are often tremendous differences, even among brothers and sisters. Some children wake up early and seem to need less sleep. Others become quite irritable and difficult if they do not get more sleep than the average, or if they are tired. In general, a well-planned program which provides acceptable and appropriate occupation for all the children in a family tends to reduce friction. Unless the child has adequate home supervision poor habits of studying often hamper even a good school.

Use of the Radio

With all the good there is in the radio, it should never be played during study hours as this produces a division of interest. Occasionally students fail in their studies because they were trying to study and listen to Bing Crosby or Bob Hope or Information Please at the same time. It can't be done. The child should do one or the other. Bing or Bob will always beat the book, which is only natural. To do one thing consciously and another subconsciously is too fatiguing.

Pitfalls of Adolescence

The child who navigates safely through childhood may encounter difficulties when he approaches adolescence. Partially solved conflicts tend to recrudescence or reappear with the added strain of physical maturing. It is well for a parent to recognize this possibility and to be equipped in advance to deal with special problems of adolescence if they arise. The same general facilities should be available in the case of adolescent problems as were serviceable to the young child. Child guidance centers and similar social agencies can be very

helpful and can adapt themselves very successfully to different age levels. It is important during adolescence to give the boy or girl legitimate outlets for growing energy without overtaxing strength.

The problem of "petting" or "necking" deserves an encyclopedia all to itself and cannot be dealt with even briefly here.

Preparation for Marriage

After adolescence the next step in an individual's emotional life is concern with marriage, preceded by the stage in which boy friends or girl friends are important. Several colleges have now included excellent courses on marriage in the curriculum. This is a great step forward and seems a splendid idea, especially since previously the scant formal preparation for marriage that was offered was usually just a sop to those girls who were disinterested in (or incapable of) higher education in a more academic form. Brides' schools formerly were concerned largely with recipes and housekeeping which, although important, are certainly no more important than the emotional understanding and acceptance of the obligations of marriage. A less housewifely and more coeducational approach to the problem of marriage also offers the future husband an opportunity to learn to participate in the phases of marriage for which husbands have heretofore had no special training. The tired business man (and all the other tired men) might learn to be less tired if they were better able to cope with the home situation and, therefore, felt less need to use work as a drug or as an escape from home or marriage. Lack of preparation for and understanding of marriage as one condition of living together (particularly in its sexual aspects) brings on or leads to more divorces (or a status of holy deadlock) than all the known physical diseases put together.

It is not yet possible to apply the science of *genetics* to courtship, but young people should be taught at least the names of the qualities they should look for in a mate. Too many women overvalue marriage and have no perspective on it or themselves and are ready to leap into it at the drop of a

hat so long as their partner wears trousers, irrespective of his limitations. An example of this is the woman who marries an alcoholic with full knowledge of his excessive drinking habits. She may deserve some part of the results of such a marriage, but her children do not deserve the sort of father and home they get.

Possibilities of Group Psychotherapy

If, after such preparation for living, a person still finds himself inclined to retreat into neurosis when faced with new problems, several possibilities present themselves. The first and most obvious, of course, is that he may see a psychiatrist or psychotherapist, if one is available in the community. In some cities clinics for group psychotherapy have been established. In these, a doctor gathers into a sort of class a number of patients who have come to him with psychological problems. They may then pool what understanding and insight they have gained by treatment and experience for their mutual benefit. This method has obvious disadvantages, but its low cost makes it available when no other form of mental help can be obtained.

Group therapy is one form of therapy that has not been adequately utilized. Its unusual value has been pointed out by Dr. Joseph H. Pratt, who originated the first and most permanent of the group clinics at the Boston Dispensary. Since Dr. Pratt demonstrated its usefulness and its practical features, his ideas have been taken up and have been developed in several other cities. An extraordinary form of social psychotherapy (with special personal and individual features) is possible in the repeated meetings and conferences of a group of Dr. Pratt's patients. There is a sort of communal or mass therapy available, which has been shown repeatedly to benefit many of those who attend the clinic.

The Management of the Menopause

At the beginning of middle age or menopause, new problems may appear, just as they did before at puberty. Certain neurotic women (and some men) get especially frantic about that time, particularly people who invest all sexual manifes-

tations with the horror and guilt they feel over their own sexuality. But this period is not actually half so terrifying as a previous generation was led to believe. Besides unmasking many of the old bugaboos associated with middle age, modern science has also discovered new uses for certain glandular extracts which tend to decrease the physical symptoms of the menopause and, from the psychological point of view, if a person has reached a sound emotional footing before middle age, he or she need not fear its onset. If he has not been able to adjust himself by that time, then one can again suggest the resources of psychotherapy. Various kinds of treatment and well-planned programs will tend to reduce anxiety and other neurotic symptoms at any age; if not directly, then indirectly by encouraging the flow of energy into non-neurotic or less neurotic channels. It is surprising to see how much judicious psychotherapy can offer certain aging neurotic individuals, and how well some persons respond to simple measures.

If after all this the individual has still managed to maintain a neurotic outlook, there is one solution fate may afford him—that is the hope that he may sink gracefully into his old age still enjoying the neurosis as much as its secondary gain will permit. And sometimes this is considerable. One may as well realize that if the neurotic individual has clung to his patterns so tenaciously for all these years, he probably likes them better than he would like anything else. He may by then be too old to change, or so rigid that change is impossible. It is a mistake to tamper psychotherapeutically with persons who are too old or too rigid to benefit by psychotherapy.

GENERAL CONSIDERATIONS OF A MENTAL HYGIENE PROGRAM

What has been described above is a large order, but it is not one that is impossible to carry out. It is a program, however, that is progressive, educational and constructive. It aims basically at attaining and maintaining a constructive and co-operative attitude and plan for living. It calls for cooperation between any given individual and those on whom he depends

for aid and guidance as he tries to grow up, face reality and be happy and useful. These are (in order) the parents, physicians (especially the obstetrician and the pediatrician) and the other persons with whom any individual comes into contact as he moves along the production line from birth to maturity. The most important and the one essential primary element that conditions all this program is a basic attitude of friendliness, fairness and constructiveness without which any psychotherapeutic program collapses.

THE PSYCHIATRIST AND THE CONTROL OF AGGRESSION

If those who are interested in furthering mental hygiene wish to go from the particular to the general and are still looking for jobs to do in the future, the most important subject for consideration is *aggression as a force in groups of people* as well as in individual human beings. This one task for psychiatric investigation in the future is clear. Someone should undertake to study examples of aggressiveness to show how it operates for destruction in groups as it does in individuals and how it can be turned into constructive paths for groups as it can for individuals. Think of the difference there might be in history if Hitler, for example, had come under the benevolent influence of any good European psychiatrist when he was a frustrated artist in Munich, one short generation ago! The effect of this kind of applied psychiatry on nations and groups of people is not assured, but it has never been applied and it should be applied. Certainly desperate individuals adopt desperate measures, whether they be artists or politicians, alcoholic or suicidal cases. It is in relation to the idea of aggression (and frustration) that physicians are now beginning to realize that the alcoholic is a sick man, and that the suicidal person is also sick, emotionally sick. Such persons should be studied more, in all ways, and efforts should be made to treat them. It is quite possible that a great deal can be done to prevent alcoholism and the occurrence of suicidal states as well as other forms of neurotic or psychotic behavior by the proper guidance of human energy in the light of preventive psychiatry and mental hygiene.

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2. Children should be taught to relax, and to concentrate when necessary.

3. Parents should remember that children are not their playthings to be poked at and tossed about.

4. Children are assets; raising them is a serious business.

5. Parents should give their children a sense of security in the child's own small world.

6. All along the production line the parent should guide the child and try not to let him go off the track of normal development. For example: it is very important for a boy (or a girl) to keep abreast of his group and be able to do what his friends can do. Every boy should know how to run and throw a ball and play with his playmates. If a boy has trouble throwing a ball, then have someone teach him. If a child does not accept guidance easily from within the family, it can come from outside. A parent can always go to the local high school and get a boy from the baseball team to come one afternoon a week until the child gets the hang of it.

7. Parents should not trust a school or camp entirely to handle the child's problems. Parents should check up on schools and camps.

If a child does not hold his own in his own world, he may become seriously atypical. He may slink off on the sidelines of life or become critical or destructive and develop inferiority feelings or escapist or defeatist attitudes. He may then more easily become a neurotic or an alcoholic or a suicidal individual.

In times like these especially, the child must be recognized not only as the future soldier or the future mother of soldiers but as the ultimate unit in democratic civilization. War itself may be considered as a kind of mass neurosis resulting from the unleashed aggression of social groups, and by this token it may be hoped that some day international mental hygiene (or its political equivalent) may play some part in preventing war, just as Woodrow Wilson once dreamed and as Roosevelt and Churchill are now planning. If such a day ever comes, if such an era is ever brought about, it will not be an accident but it will be a condition that has been purposively achieved by methods and with direction.

The importance of studying aggression in its personal and social forms cannot be overemphasized, especially to teachers and ministers and all who work with groups. If parents, teachers, ministers and doctors understand the problem of aggression adequately, its tide might possibly be turned from where it arises into constructive channels. If there is one single psychological basis at the root of many forms of neuroses and psychoses, it may quite possibly be some disturbance or imbalance leading to the improper spending of energy and the misdirection of aggression. Energy may flow into many kinds of channels. It may be spent destructively against one's self or destructively against others, or it may be constructively released. Energy constructively spent almost inevitably implies a constructive attitude toward the outside world since a truly constructive person cannot remain an individual unit but by necessity must become socially involved in one way or another. The idea of controlling aggression and using it constructively can be much further applied by parents and teachers to children and young adults in helping them grow up and become well adjusted. One thing is certain: There will never be a better world than the people who live in it.

THE MENTAL HEALTH OF THE CHILD; ITS IMPORTANCE TO THE FUTURE

Naturally one might inquire: What has all this to do with the prevention of neurosis? The answer to this question is not obscure. Here it is: If the influence of early life on the later ultimate personality is apparent, then it follows that the efforts of the mental hygienist should be directed as much as possible toward preventive work at early stages in the life of the individual. Psychiatry has been concerned too long merely with diagnosis, description and custodial functions. As a science, psychiatry has passed its initial stage and must now apply some of the knowledge that has been acquired at such great cost.

First of all, the child, as an individual, must come into his own. In concrete terms this means that:

1. Parents should not overexcite children.

2. Children should be taught to relax, and to concentrate when necessary.

3. Parents should remember that children are not their playthings to be poked at and tossed about.

4. Children are assets; raising them is a serious business.

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